THIS NUMBER COMPLETES VOLUME XLV

Medical Library

BULLETIN

OF THE

JOHNS HOPKINS HOSPITAL

DEC 13 1929

(THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL)

(SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY)

Vol. XLV, No. 6 DECEMBER, 1929

Contents

The Pathogenesis of Glomerular Nephritis. WARFIELD T. LONGCOPE, M.D. 335

The Effect upon Haemolytic Streptococci of Cultivating Them in Immune and Normal Serum. ELEANOR A. BLISS AND HAROLD L. AMOSS 361

A Study of Reflexes in the Deafferented Leg of the Cat and Their Relation to Tonus. WILBUR L. SPRONG 371

Book Reviews 396

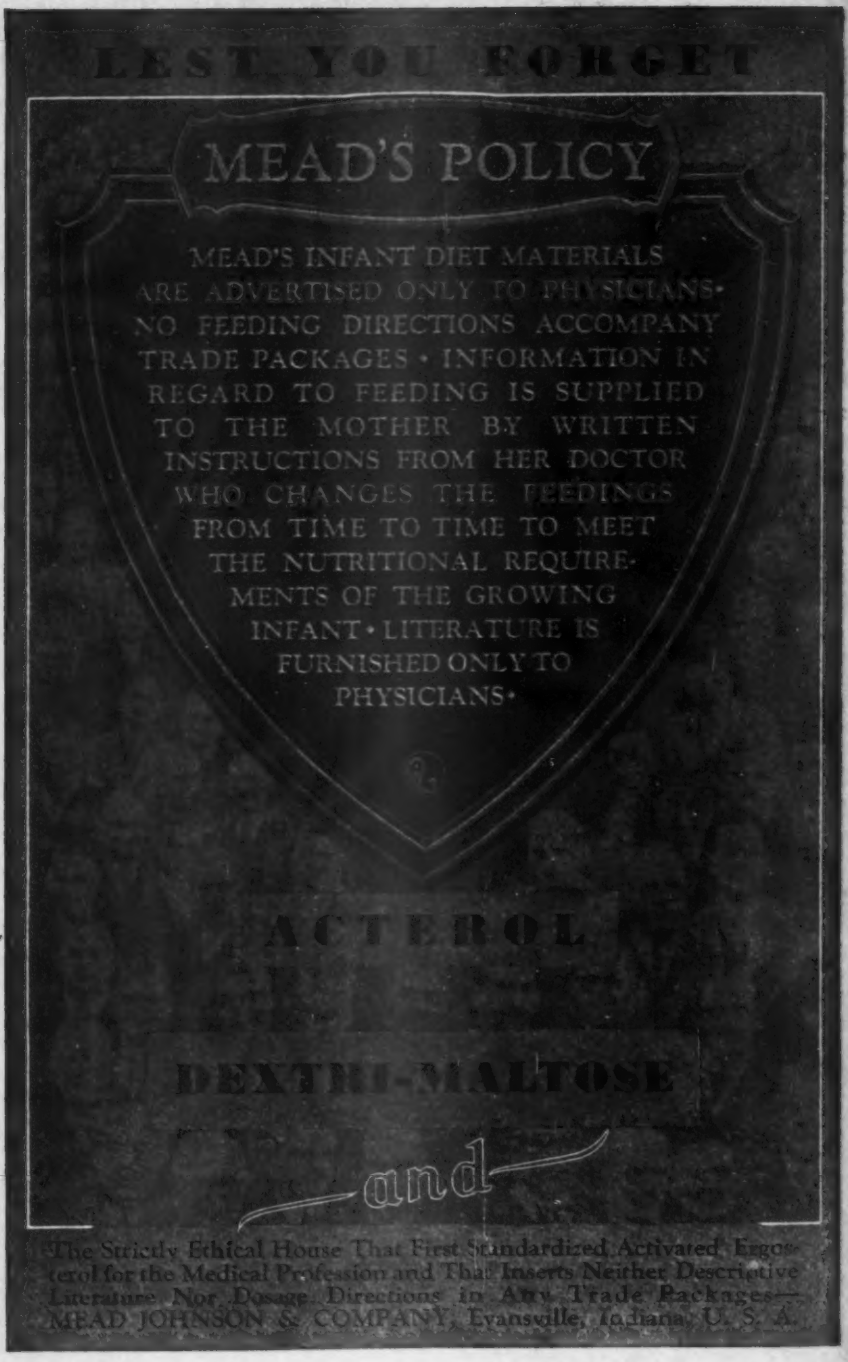
Index 403

PUBLISHED MONTHLY

THE WILLIAMS & WILKINS COMPANY

BALTIMORE, U. S. A.

Made in United States of America


LEST YOU FORGET
MEAD'S POLICY
MEAD'S INFANT DIET MATERIALS ARE ADVERTISED ONLY TO PHYSICIANS· NO FEEDING DIRECTIONS ACCOMPANY TRADE PACKAGES · INFORMATION IN REGARD TO FEEDING IS SUPPLIED TO THE MOTHER BY WRITTEN INSTRUCTIONS FROM HER DOCTOR WHO CHANGES THE FEEDINGS FROM TIME TO TIME TO MEET THE NUTRITIONAL REQUIREMENTS OF THE GROWING INFANT· LITERATURE IS FURNISHED ONLY TO PHYSICIANS·
ACTEROL
DEXTRI-MALTOSE
and
The Strictly Ethical House That First Standardized Activated Ergosterol for the Medical Profession and That Inserts Neither Descriptive Literature Nor Dosage Directions in Any Trade Packages—
MEAD JOHNSON & COMPANY, Evansville, Indiana, U. S. A.

Entered as second-class matter at the Baltimore, Md., Postoffice. Acceptance for mailing at special rate of postage provided for in Section 1103, act of October 3, 1917. Authorized on July 3, 1918.
Copyright, 1929, by The Williams & Wilkins Company

THE PATHOGENESIS OF GLOMERULAR NEPHRITIS[1,2]

WARFIELD T. LONGCOPE, M.D.

Bright's disease presents problems which in many respects resemble those of heart disease. Both are common, both affect vital organs and are responsible for a large number of deaths. Both diseases are frequently chronic in nature, and, in either the heart or the kidney, a variety of anatomical changes may interfere so seriously with the function of the organ that entirely different forms of the disease may become indistinguishable in the terminal stages. During the last 30 years the complicated state called heart disease has gradually been resolved into several well defined affections, each involving the heart in a special and recognizable manner. We have in consequence come to distinguish, as separate entities, rheumatic heart disease, syphilitic heart disease, hypertensive heart disease and arteriosclerotic heart disease. The ultimate effect of all of these upon the circulation may be much the same, but each is distinct in etiology, in pathogenesis, and in its natural history.

Our information concerning Bright's disease today is in much the same state of confusion as was our knowledge of heart disease many years ago, for it is not yet clear whether we have to deal with a single process presenting itself both to the clinician and to the pathologist in a variety of forms, or whether under the term Bright's disease there are included several separate and distinct entities related only in so far as they produce bilateral non-suppurative lesions of the kidneys.

Despite the fact that our knowledge of the function of the kidneys in both health and disease has been materially advanced during the last 20 years, and although more recently we have learned much concerning the chemical and physical chemical alterations in the body fluids during the various stages of kidney failure, we have not obtained much precise information concerning the etiology of Bright's disease,

[1] Fourteenth Mellon Lecture before the Society for Biological Research of the University of Pittsburgh School of Medicine, May 15, 1929.

[2] Aided by a grant from the Ella Sachs Plotz Foundation.

and are therefore unable to unravel with any degree of success its complicated forms.

It is apparent that almost any condition which leads eventually to a uniform destruction of a large part of both kidneys will finally result in serious impairment of the functions of these organs. Derangement of the function of the kidneys, whether it be rapid or gradual, is accompanied by profound changes that affect the body as a whole. The dramatic and complicated conditions such as oedema, hypertension, acidosis and anaemia that are so frequently associated with renal failure have presented fascinating and important problems for investigation; and our understanding of the pathological physiology and chemistry of renal failure has been considerably increased by extensive research in this field. Much of this work has led to results that have been of direct practical value, for methods have been evolved which enable us to detect the early stages of renal failure and allow us to estimate, at least roughly, the gradual or rapid progress of this failure.

The ultimate cause or causes of Bright's disease, however, and the resolution of this complex process into clearly defined and recognizable entities, if there be such, still remains an important problem for solution. Even our attempts to classify the disease by forms must be purely temporary, and, until our comprehension of nephritis becomes clearer, must be regarded as a scaffolding upon which to build more substantially.

Bright (1) in 1827 gave the first descriptions of one great group of cases, the diffuse nephritides, while Gull and Sutton (2) in 1872, in an account of the condition which they termed Arterio-Capillary Fibrosis, described for the first time a second important group now recognized as vascular nephritis. The subsequent and more recent work of Loehlein (3), Jorès (4), Müller (5) and Volhard and Fahr (6) has resulted in the general recognition of three great groups of kidney disease: (1) the degenerative lesions of the tubular epithelium called first by Müller nephrosis; (2) the inflammatory lesions of the glomeruli, long known as glomerular nephritis; and (3), the atrophic contractions of the kidney secondary to disease of the arteries and arterioles, known as vascular nephritis. These may be translated into such a clinical classification as that proposed by Addis (7) (a) the

degenerative; (b) the hemorrhagic, and (c) the arteriosclerotic. In spite of these rather clear cut and familiar distinctions there exists actually considerable confusion in the differentiation of these types both by the clinician and by the pathologist. At autopsy it is uncommon, especially in elderly persons, to encounter uncomplicated examples of any one of these forms, for, as a rule, though one or another may predominate, it is the general impression that combinations of any two or all three are usual.

In order to make material progress, therefore, in our knowledge of this subject it has seemed to us necessary to concentrate on one form of nephritis, endeavoring to study this form from its inception through the different phases of its development, either to recovery or to the progressive chronic stage and death. For this reason we have chosen the glomerular type, which in its characteristic form is seen at autopsy as a peculiar inflammatory process affecting the glomeruli, but also involving frequently the interstitial tissue about Bowman's capsule. There has been sufficient study of a clinical picture in correlation with the pathological picture of glomerular nephritis to allow us to recognize during life with a relative degree of accuracy the early stages of this form of Bright's disease. The late stages, or chronic forms, on the other hand, in which the functions of the kidney are much impaired, may simulate so closely the advanced nephroses and vascular nephritides that a clear differentiation in the clinic may be very difficult or at times impossible. Two problems above all others have absorbed our attention: (1), the etiology of acute glomerular nephritis which is a matter of the utmost importance, and (2), the natural history of its course, for one must know the phases of its progress in order to recognize the form in its chronic stage.

At the outset one must understand that two separate forms of acute glomerular nephritis are distinguishable. One first termed by Loehlein (8) *acute focal glomerular nephritis*, the other known as *acute diffuse glomerular nephritis*.

In the focal type of glomerular nephritis, whether it be embolic or simple in form, the kidney at autopsy is not found to be affected as a whole. Baehr (9) has described extensively the lesions in embolic glomerular nephritis. Minute hemorrhages may fleck the surface of the kidney, and these on microscopic section are found to be con-

nected with groups of tubules and isolated glomeruli, which show inflammatory lesions, haemorrhage, necrosis or thrombi, sometimes containing bacteria, in one or more of the capillary loops. The disease is rarely recognizable except through an examination of the urine. In mild cases there is no oedema or hypertension; the retina is unaffected, headache, nausea and vomiting are absent, and the function of the kidney is not sufficiently impaired to interfere with the excretion of salt, water, 'phthalein and non-protein nitrogen. The damage to the kidney is best determined by the condition of the urine. There is excretion of albumin, of red blood cells, often in great amount, of leucocytes and moderate numbers of casts; and the urinary picture alone reflects the injury inflicted on the isolated glomeruli. With repeated attacks of this form of focal lesion, so many glomeruli may be damaged that the function of the kidney becomes materially impaired and then the process, both anatomically and clinically, resembles very closely the diffuse glomerular nephritis which will be considered more fully later.

The focal glomerulitis, as far as is known, is always an accompaniment of an acute infection, and the embolic form occurs most characteristically in bacterial endocarditis. The lesions in the kidney are quite analogous to the petechial haemorrhages seen over the skin and elsewhere in the body, and as it is possible in the vast majority of such cases to cultivate the same organism from the urine as is found in the circulating blood and as clumps of bacteria are often found in the glomerular loops, it has been supposed that the injury to the glomeruli is produced directly by these micro-organisms. It must be pointed out, however, that conglomerations of streptococci may be found in the capillaries of glomeruli that show no other abnormality. The peculiarity of the focal embolic nephritis is that scattered isolated glomeruli or even portions of a single glomerulus are affected, and that the usual symptoms of acute nephritis are absent.

With the disappearance of the general bacteraemia the attack of glomerulitis ceases, and, as Baehr has shown, the glomeruli heal by scar-formation. The process is rarely sufficiently widespread, however, to impair permanently the function of the kidney.

Chart 1 (Case 1) represents a typical example of focal glomerular nephritis occurring in a child during the course of varicella complicated

by acute tonsillitis and caused by β-haemolytic streptococci. The patient was studied by Baker and Denny (10), and it is significant that in the presence of the pronounced haematuria with the presence of haemolytic streptococci in the urine, there should be no other symp-

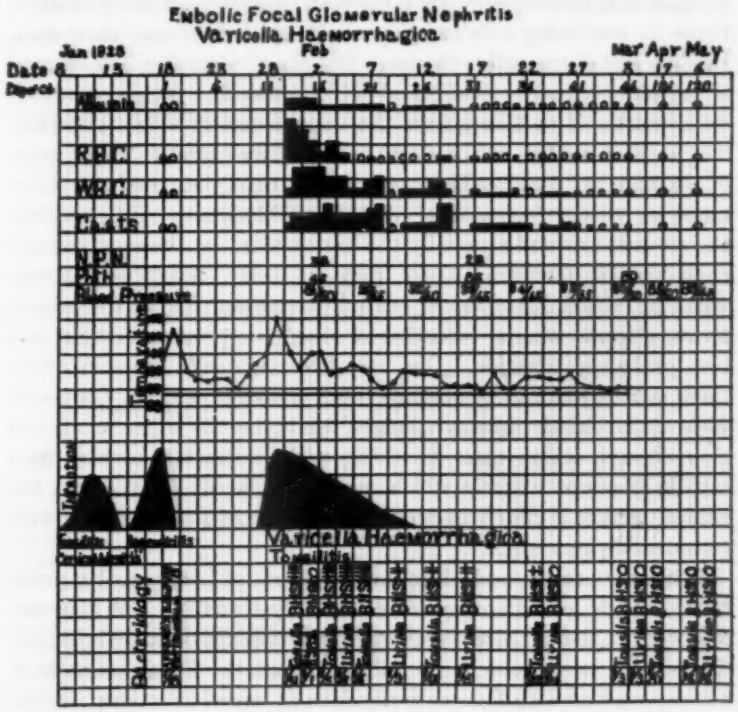


CHART I. SHOWING THE GENERAL COURSE OF THE DISEASE, WITH THE AMOUNT OF ALBUMIN, BLOOD, CASTS IN THE URINE, CHARTED IN RELATION TO THE BACTERIOLOGY OF THE TONSILS AND URINE

toms or signs of nephritis. Recovery was complete and more than a year after the acute attack the child remains normal on examination.

Rare instances have been observed by Volhard and Fahr and by Baehr (11) in which the focal glomerular nephritis has been seen in combination with the diffuse glomerular nephritis. In these instances the condition has been termed by Volhard and Fahr the *mixed form*.

The origin of the second form of glomerular nephritis, the diffuse glomerular nephritis, is much more obscure. It is observed in its classic form as a complication of scarlet fever. Both kidneys are, as the name implies, diffusely affected. Almost every glomerulus may be more or less involved; there is often an infiltration of the interstitial tissue by wandering cells and the tubular epithelium may show some swelling and degenerative change. But the abnormality is characteristically and primarily an affection of the glomeruli, a peculiarity which differentiates it definitely from the other forms of Bright's disease. The onset is sudden, with oedema and with the excretion in the urine of albumin, red blood cells, leucocytes and casts composed of hyaline material, leucocytes, epithelial cells and red blood cells. The oedema, the albuminuria and especially the haematuria, are the constant and characteristic features. There may be fever, headache, nausea, vomiting, visual disturbances, acute hypertension, and in the severer forms, oliguria, anuria, retention of blood non-protein nitrogen and low 'phthalein excretion. One may encounter mild cases in which there is little more to be observed than transient oedema, associated with characteristic urinary changes; while, on the other hand, one may observe severe cases in which, with protracted anuria, there rapidly develops uraemia which terminates fatally. As a rule, the clinical picture is clearly defined and the diagnosis can be made with considerable accuracy.

It has been recognized, since the early work of Loehlein, that acute haemorrhagic nephritis may follow not only scarlatina, but may also follow or be associated with several other varieties of acute infection. Of these the most common is tonsillitis. though the disease is known to accompany such infections as erysipelas and wound infections. Loehlein and all recent observers have emphasized the fact that acute haemorrhagic nephritis is especially prone to complicate infections that are caused by streptococci. On the other hand, many authorities can find no direct connection in many instances between an obvious infection and the onset of acute diffuse glomerular nephritis.

It therefore seemed essential to direct particular attention to this point and by careful investigation of as large a series of cases as possible to determine in what proportion the onset of the disease was associated with an acute infection, and furthermore to isolate the organism responsible for the infection present.

Table I shows the results of this investigation, carried out with Drs. Hansen, Denny, O'Brien and Lukens, in 55 cases of acute and subacute nephritis and includes 15 additional cases added since the first publication (12).

Table II shows the form of infection and the type of infecting organism discovered in 48 of these cases.

TABLE I

Incidence of acute infections at onset or during course of 55 cases of acute and subacute nephritis

NUMBER OF CASES	INFECTION PRESENT		INFECTION ABSENT	
	Number	Per cent	Number	Per cent
55	48	86.3+	7	12.7+

TABLE II

Bacteriology of infections at onset of 48 cases of acute and subacute glomerular nephritis

FORM OF INFECTION	NUMBER OF CASES	BACTERIA PRESENT				NO CULTURES; NO PREDOMINATING BACTERIA
		Strep. haemoly. β Type	Strep. haemoly. α Type	Pneumococci	Pfeiffer's bacillus	
Tonsillitis	24	16	5			3
Sinusitis	13	7	2	1	1	2
Scarlatina	4	2				2
Otitis media, bronchitis, and pneumonia	4	3				1
Infection of wounds and lymph nodes	3	3				
Total	48	31	7	1	1	8

It is obvious from Table II that infections, particularly of the tonsils and sinuses, are very common at the onset and during the early stages of acute nephritis. Sinusitis, unlike tonsillitis, is sometimes difficult of detection, and extensive purulent infection of the sinuses may be discovered only by special methods of examination. We have been fortunate in having the cooperation of Dr. Crowe, without whom it would have been impossible to make these special studies. It is also very important to note that the majority of these infections were caused by haemolytic streptococci. This fact cannot fail to lead one

to hypothecate a close analogy between the origin of these cases of acute glomerular nephritis, and those complicating scarlet fever, for it is now known that scarlatina is caused either by a special type of β-haemolytic streptococcus or one capable of producing a very potent "toxin." Though the evidence is not as yet conclusive, there is much to uphold the view that a localized infection by haemolytic streptococci may in some way precipitate an acute attack of diffuse glomerular nephritis. The correlation between the two is at least sufficiently well established to form the basis for future experimentation along this line.

Direct experimentation, so far, has not yielded conclusive corroborative results. Lesions in the glomeruli of animals sometimes described as glomerular nephritis have occasionally been observed following the intravenous injection of streptococci. Ophüls (13) used rabbits, Kuczynski (14) used mice, and Bell, Clawson and Hartzell (15) used monkeys, while a characteristic focal glomerular nephritis has been produced in dogs by Kinsella and Sherburn (16), and by Clawson (17). Duval and Hibbard (18), Gray (19), and more recently Rich, Bumstead and Frobisher (20) have described injury to the glomeruli of rabbits with haemorrhage into the glomerular capsule by the intravenous injection of filtered products of the growth of streptococci, but so far it has not been possible to reproduce in animals the characteristic diffuse glomerular nephritis of man.

It is consequently necessary to continue such investigations in the clinic, and in order to obtain further information an effort was made to determine in what way a local streptococcus infection in man might produce diffuse glomerular lesions.

There is no evidence to show that diffuse glomerular nephritis is caused either by the lodgment of streptococci in the glomerular capillaries, or by the direct action of bacteria in the kidney. Careful and repeated cultures from large amounts of urine in these patients have yielded negative results. Cultures from the blood stream at the onset of the disease and during its course have given negative results, and streptococci have not been found in sections of the kidney.

There is a popular conception that toxins elaborated by streptococci at the site of the infection and excreted through the kidney may be directly responsible for the kidney lesions. Though we have, in general,

little information about the excretion of bacterial toxins through the kidney, it is known that the specific soluble substance obtained by Avery and Heidelberger from pneumococci is frequently found in the urine during the course of lobar pneumonia, while Trask and Blake (21) have found that the urine in some cases of scarlatina will give a skin reaction similar to the "Dick toxin." We have endeavored to detect similar substances in the urine of cases of acute nephritis, but it soon became evident in this work that albuminous urine frequently caused non-specific skin reactions, and so far it has not been possible to eliminate this source of error through technical manipulations. In one instance, however, of acute tonsillitis followed by acute nephritis,

TABLE III

Table of post-scarlatinal complications—Schick

	PERIOD FOLLOWING ONSET								TOTAL	
	2 weeks	3 weeks	4 weeks	5 weeks	6 weeks	7 weeks	8 weeks	10 weeks		
Lymphadenitis	2	37	22	6	1				68	
Nephritis	2	18	7	3	3				33	
Post-scarlatinal fever	1	20	9	2	1				33	
Relapse: Cases, author's	1	3	6	2	1				13	71 relapses
Relapse: Cases, in literature	10	18	16	8	4		2		58	
Total	16	96	60	21	10		2		205	

the urine in 1 to 10 dilution produced a skin reaction in susceptible persons at a time when the albumin was minimal in amount. After tonsillectomy the urine no longer gave this reaction

It is possible, though not proven, that the products of the growth of haemolytic streptococci responsible for such infections as tonsillitis and sinusitis may be eliminated through the kidney. If the nephritis is to be ascribed to the direct action of these toxins upon the kidney cells, the changes in the kidneys might be expected to appear during the early stages of the infection, whereas by determining the time of onset of the nephritis in relation to the time of onset of the infection, as is possible in scarlatina, it is found that the acute nephritis starts usually during convalescence and appears as a rule three to four weeks

after the onset of scarlatina. Schick (22) observed (Table III) that other specific complications such as lymphadenitis, recurrent fever and actual relapse were most likely to occur during this same period.

Though it is difficult to measure with accuracy the time interval between the onset of tonsillitis or sinusitis and the onset of nephritis, it rarely happens that the two conditions appear simultaneously, for the first symptoms and signs of acute nephritis are usually observed during convalescence or at least several days after the onset of the acute infection. Indeed, these time relationships led Schick, and later von Pirquet (23), to draw an analogy between the specific complications of scarlet fever, such as acute nephritis, and the occurrence of serum disease following one to two weeks after the therapeutic administration of horse serum. From this analogy they conceived the idea that post-scarlatinal nephritis might be explained as a manifestation of heightened susceptibility of the individual to the infection. Pirquet later used the word *allergy* to signify this particular state. At the present time it is becoming more and more obvious that in streptococcic infections, as in tuberculosis and syphilis, an induced allergy to the proteins of the streptococcus or to the products of its growth may account for some of the symptoms of the infection and for certain variations in the course of the disease. The original idea expressed by Bristol (24) that the exanthem of scarlet fever is an allergic reaction to the local streptococcic infection in the throat has been upheld by the recent observations of Dochez and Stevens (25) and of Cooke (26). It has further been shown by Cooke and by Dochez and Stevens that the Dick reaction is not a simple reaction to a toxin such as occurs with diphtheria and tetanus toxin, but is in part dependent upon sensitization of the individual to the products of the growth of scarlatinal streptococci. There are, thus, similarities between the Dick reaction and the tuberculin reaction, but unlike tuberculin the Dick toxin is neutralizable by specific antisera and by the serum of patients convalescing from scarlatina. It is known that during convalescence from scarlatina the Dick reaction, previously positive, rapidly decreases in intensity and soon becomes negative; and it is assumed that the disappearance of the Dick reaction is dependent upon the accumulation of neutralizing substances in the blood serum and tissue fluids.

It is of importance to learn whether any pronounced variation in this course of events may occur in patients suffering from scarlatinal nephritis. Friedemann and Deicher (27) have recently contributed some observations on this point, and state that the Dick reaction disappears as rapidly in patients suffering from post-scarlatinal nephritis as it does in those suffering from uncomplicated scarlatina. In spite of the fact that the Dick reaction was negative in the cases of scarlatinal nephritis which they studied, they are nevertheless inclined to relate the lesion in the kidney to an allergic reaction in the body, and believe that it can be linked with the precocious formation of an antibody which they can demonstrate in the serum during convalescence, and which has the property of protecting mice against infection by streptococci.

We have observed, as have others, that the filtered broth cultures of the haemolytic streptococci, recovered from the tonsillar and sinus infections in our cases of acute and subacute nephritis, give rise to skin reactions similar to the Dick reaction. As a rule, the potency of these filtrates is not great, and, unlike the toxins, with which we are familiar, they are very resistant to heat. In studying the skin reactions produced by these filtrates, it was soon noted that unusually intense reactions occurred in patients with acute and subacute glomerular nephritis.

With Dr. O'Brien, Dr. Hansen and Dr. Lukens I undertook to investigate this matter in more detail. The procedure was somewhat tedious for it was found necessary to test the skin to many filtrates, since some persons reacted to one and some to another filtrate.

The number of individuals tested is therefore not very large. We studied two groups of cases as controls, (1) normal individuals or those suffering from a miscellany of conditions, and (2) a group of cases of tonsillitis, since it was desired to know whether exaggerated skin reactions might be dependent solely upon the presence of an acute streptococcus infection.

Table IV shows in summary the results of these investigations. From these figures we may conclude that there is some increased tendency beyond the normal for patients suffering from acute tonsillitis to show mild skin reactions to the filtrates, but a very pronounced tendency for many patients with acute and subacute nephritis to give

exaggerated reactions. Whereas the normal individual may react positively with dilutions of 1 to 100 filtrate, many of the nephritic patients react strongly with dilutions of 1 to 2000.

It seems justifiable to conclude from these observations that a considerable number of cases of acute and subacute nephritis give exaggerated skin reactions to bouillon filtrates of haemolytic streptococci, and it seems further probable that this pronounced reaction means that these patients have acquired or possess a high degree of allergy towards some substance in haemolytic streptococci or in the products of their growth. We have found, moreover, that this is not a temporary phenomenon but one that may persist throughout the acute attack of nephritis, or even for several years after the patient

TABLE IV

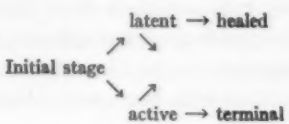
Summary of skin reactions

DIAGNOSIS	TOTAL CASES	TOTAL +	PER CENT	TOTAL ++++	PER CENT
Controls	60	38	62.2	15	25.0
Tonsillitis	22	21	95.4	4	18.1
Nephritis	27	22	81.4	18	66.6
	TOTAL TESTS				
Normal	542	167	30.8	33	6.0
Tonsillitis	123	70	56.9	4	3.2
Nephritis	259	162	62.5	62	23.9

has recovered from his infection and apparently from his attack of acute nephritis.

It is almost as difficult to understand the progress of acute glomerular nephritis as it is to determine its etiology. A certain proportion of patients, especially young children, may recover and one can best indicate the possible progress of the disease by the following chart which Addis uses:

The possible resolution of glomerular and hemorrhagic nephritis



The so-called latent or inactive stage may last for only a few weeks before recovery ensues, or it may persist for years before terminating in an actively chronic stage and death. Whether the untoward progress of glomerular nephritis occurs uninterruptedly or irregularly through repeated mild exacerbations is not definitely known, though we have some observations which suggest that the latter method is more common. It is manifestly difficult, however, to obtain exact and detailed information about the natural history of a disease which may persist in a mild or inactive form perhaps for years, without causing symptoms that annoy the patient, and without producing signs other than those that can be detected by a detailed and often elaborate examination.

Probably on this account there is comparatively little information based even on rough statistics of the precise outcome of attacks of acute glomerular nephritis. James (28) examined 67 children, from 3 months to 15 years after an acute attack of nephritis, the average interval being 5 years. He found that in only 9, or 13.3 per cent, had the termination been in a chronic form of the disease. Hansborg (29) examined 284 children one to ten years after they had had an attack of scarlatinal nephritis, and could find no abnormalities in 259. Twenty-three were said to show orthostatic albuminuria, one persistent albuminuria, and one was suffering from chronic nephritis.

The observations of Hume and Nattras (30), of Deutsch (31) and of Siguret (32) and Magnus-Alsleben (33) on the outcome of war nephritis occurring in the British, French and German armies show that complete recovery from acute nephritis is not so common in the adult as in the child, and our experience is in accord with this conclusion. The cases may be divided into three categories, (1) healed (patient well): those patients in whom no abnormality can be found either on physical examination or by examination of the urine; (2) inactive: these patients are symptomless and present no definite physical abnormality but still show traces of albumin, occasional red blood cells and a few casts in the urine; (3) active or progressive: these patients show such physical abnormalities as elevation of blood pressure, enlargement of the heart, oedema of varying degrees and alterations in the retina, combined with definite abnormalities in the urine. In the last group are included the fatal cases.

Table V, which includes the patients that we have studied, shows figures indicating perhaps roughly the relative proportion of recoveries as compared with the inactive and progressive cases.

From these figures it is seen that apparently somewhat less than half the adult patients recover completely from an attack of acute nephritis.

TABLE V

Progress of acute nephritis in adults

AUTHOR	TOTAL CASES	WELL		PROGRESSIVE? LATENT		PROGRESSIVE ACTIVE	
		Number	Per cent	Number	Per cent	Number	Per cent
Hume and Nattras	281	128	45.5	126	45.0	27	9.5
Deutch	200	99	49.5	43	21.5	58	29.0
Siguret	47	8	17.0	22	46.7	17	36.3
Magnus-Alsleben	?		40.0		25.0		35.0
W. T. L.	29	12	41.4	4	13.8	13	44.8

TABLE VI

Relationship of course of nephritis to persistence of infection (followed 4 months to 7 years)

CONDITION	NUMBER OF CASES	CULTURES	
		Positive	Negative
Well	12	2	10
Inactive	4	2	2
Progressive	13	11	2
Total	29	15	14

It is, of course, an extremely important matter to discover what factors may determine the outcome of the acute nephritis. If the acute infection was directly responsible for the onset of the acute nephritis it seemed probable to us that a continuation of the infection or of the infecting organism might be responsible for the progression of the disease to a chronic state; while elimination of the infection and the infecting organism might be expected to result in recovery. With this idea in mind we have succeeded in following the course of the infection, together with the course of the nephritis, with some degree of accuracy, in 29 of our patients for periods varying from 8

months to 7 years. During this time these patients have been examined every few months and at the same time cultures have been made from existing infectious lesions, or from the throats and nasopharynx of the tonsillectomized patients.

The results of this study may be seen in the Table VI.

The observations show that a large proportion of the patients that are now well have remained free from infections due to β-haemolytic streptococci over long periods of time. One of the healed cases, a patient in whom acute tonsillitis preceded the acute nephritis, and in whom tonsillectomy was performed during convalescence, has shown on a single occasion over a period of two years a few β-haemolytic streptococci in the nasopharynx. The second healed case, one of acute tonsillitis and sinusitis due to β-haemolytic streptococci, has had several mild attacks of bronchitis, caused by micro-organisms other than β-haemolytic streptococci, and has recently suffered from one such attack caused definitely by β-haemolytic streptococci without, so far, any indication of recurrence of nephritis.

In the inactive cases the patients have, from time to time, had mild infections due to haemolytic streptococci, or positive cultures with continuous slight signs, such as moderate hypertension, slight albuminuria and the presence of occasional red blood cells and hyaline casts in the urine.

The majority of the progressive cases, four of these patients having died, have had continuous and obvious infections of the paranasal sinuses or nasopharynx, from which cultures have shown persistently, or at irregular intervals, great numbers of haemolytic streptococci. One patient, whom we have included in this group, and in whom the acute nephritis was associated with an acute cervical adenitis caused by β-haemolytic streptococci, died during the acute stage of the disease from a complicating lobar pneumonia due to *Pneumococcus* type IV.

The actual course of the disease in these three groups of cases can best be indicated in charts.

Chart II (Case 2) shows the course of the disease in one patient who has recovered and is now well three and a half years after his primary attack.

Besides demonstrating the general course of the nephritis in relation

to the activity and disappearance of the infection, it indicates a close relationship between exacerbations of the acute infection and exacerbations of the nephritis; for on the 23rd of February, 1926, following the tonsillectomy, there was a streptococcus infection of the nasopharynx associated with a definite increase in symptoms of the nephritis. This we have observed so frequently that we are inclined to attribute to it considerable importance. Operative procedures upon the sinuses

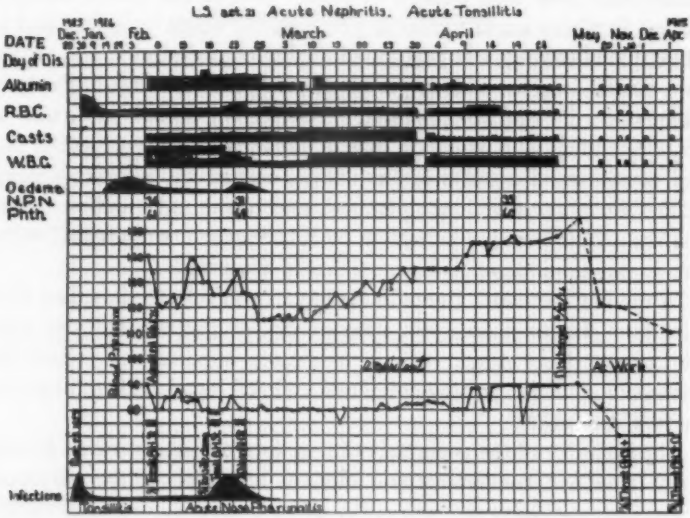


CHART II. CASE 2, SHOWING THE RESULTS OF URINE EXAMINATIONS, THE NON-PROTEIN NITROGEN OF BLOOD AND PHTHALEN EXCRETION, THE CHANGES IN SYSTOLIC AND DIASTOLIC BLOOD PRESSURE, THE BACTERIOLOGICAL EXAMINATIONS AND COURSE OF THE INFECTION CHARTED CHRONOLOGICALLY

have almost invariably been followed by increased haematuria and albuminuria, and sometimes by the return of oedema and rapid elevation in blood pressure. Tonsillectomy has more rarely been accompanied by similar results. These signs of exacerbation are usually observed within 24 to 48 hours after the surgical manipulation, but they may occur more promptly, and in one instance increased haematuria appeared four hours after operation. As a rule, the exacerbation

has been of short duration, lasting only a few days, but in a few instances the reaction has lasted much longer; and it is therefore very

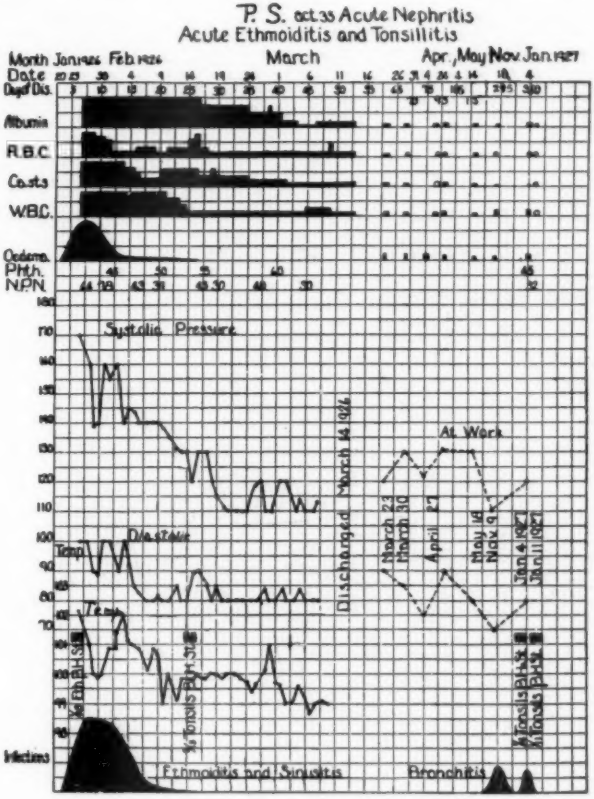


CHART III. CASE 3, SHOWING THE RESULTS OF URINE EXAMINATIONS, THE COURSE OF EDEMA, THE PHTHALEIN EXCRETION AND NON-PROTEIN NITROGEN OF THE BLOOD, THE CHANGES IN SYSTOLIC AND DIASTOLIC BLOOD PRESSURE, THE TEMPERATURE CURVE, THE RESULTS OF BACTERIOLOGICAL EXAMINATIONS AND THE COURSE OF INFECTIONS CHARTED CHRONOLOGICALLY

important that one should be fully aware of the risk that is involved in the operative removal of infected tissue in these patients.

Chart III (Case 3) indicates the condition of a patient probably in the inactive stage of the disease. Although the patient was at work and apparently well one year after a rather severe attack of acute nephritis, the urine still showed albumin and there was slight oedema about the ankles. Cultures from the tonsils which had not been

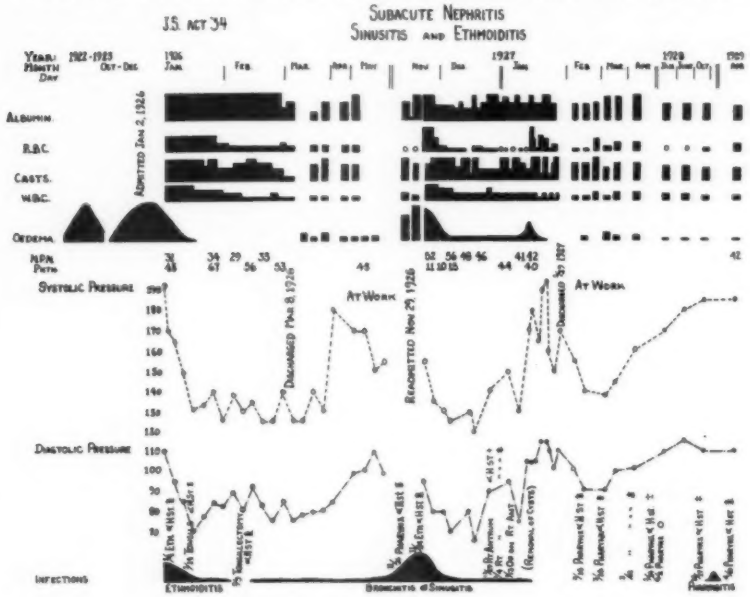


Chart IV. Case 4, Showing the Results of Urine Examinations, the Course of Oedema, the Phthalein Excretion and Non-protein Nitrogen of Blood, the Variations in Systolic and Diastolic Blood Pressure, the Course of the Infections, the Results of Bacteriological Examinations, and the Effect of Operation on the Accessory Nasal Sinuses on the Course of the Disease.

removed showed many β-haemolytic streptococci. Since January 1927 it has not been possible to examine the patient, but he is reported as being at work.

Chart IV (Case 4) demonstrates the conditions that may exist in a patient with progressive chronic nephritis associated with persistent

infection of the paranasal sinuses and nasopharynx by haemolytic streptococci.

The chart shows the earlier phases of the disease characterized by massive oedema, moderate hypertension, marked albuminuria, cylin-

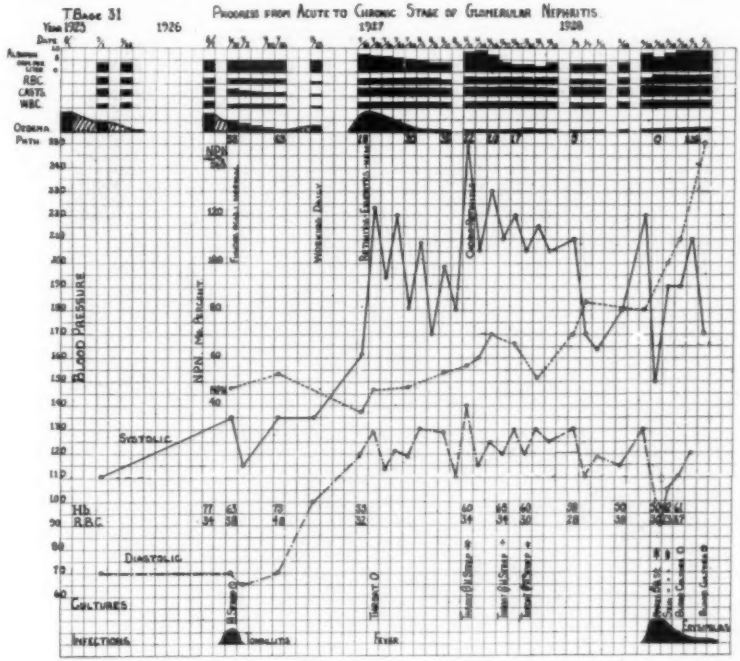


Chart V. Case 5, Showing the Results of Urine Examinations, the Course of Oedema, the Phthalein Excretion and Non-protein Nitrogen of the Blood, the Variations in the Systolic and Diastolic Blood Pressure, the Changes in Hb and Red Blood Cells, the Course of the Infections and the Results of Bacteriological Examinations.

druria and haematuria; the comparatively quiescent periods with low blood pressure and absence of oedema, interrupted by acute and serious exacerbations; the immediate results of radical operation on the sinuses; and the subsequent course with slow but definite progress to

a chronic hypertensive stage, with insignificant oedema and full capacity for work but considerable impairment of renal function.

Chart V (Case 5) shows the complete course of a case of glomerular nephritis from the acute onset to death four years later.

It is to be noted that when the patient came under observation during the acute oedematous phase there was no increase in blood pressure. With the progression of the disease, albuminuria, haematuria and cylindruria persisted, the oedema subsided, and the blood

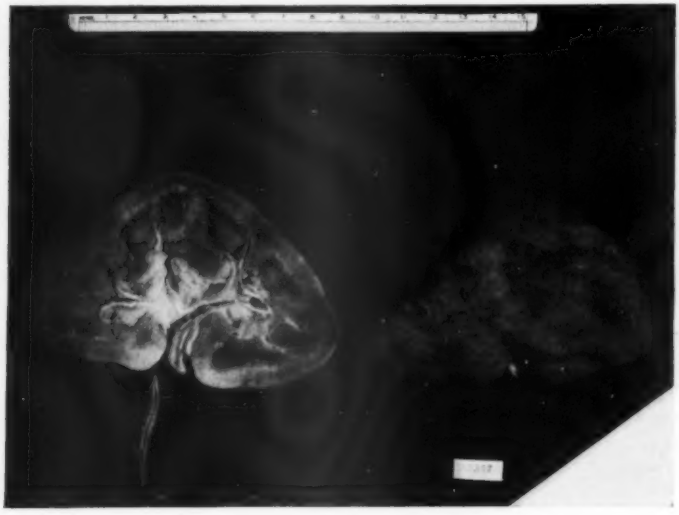


FIG. 1. GROSS APPEARANCE OF KIDNEYS FROM CASE 5

pressure rose. At the same time the 'phthalein excretion diminished, the blood non-protein nitrogen rose, and anaemia appeared. In spite of the tonsillectomy, β-haemolytic streptococci were found, from time to time, in the throat, and erysipelas terminated the disease in uraemia.

The kidneys (Figs. 1, 2, and 3) showed at autopsy an advanced stage of glomerular nephritis. There was practically no involvement of the arteries or of the arterioles of the kidney or of other organs.

The charts from these four cases serve to illustrate the various phases

of the progress of diffuse glomerular nephritis from the acute stage first, to recovery; secondly, to an inactive stage; thirdly, to the chronic progressive stage and, finally, to death. The unfavorable progress may pursue its course very slowly with long periods of inactivity, or more rapidly, with short periods of comparative inactivity in which the oedema disappears, the blood pressure becomes normal and the patient is symptomless, but in which the urine continues to show much

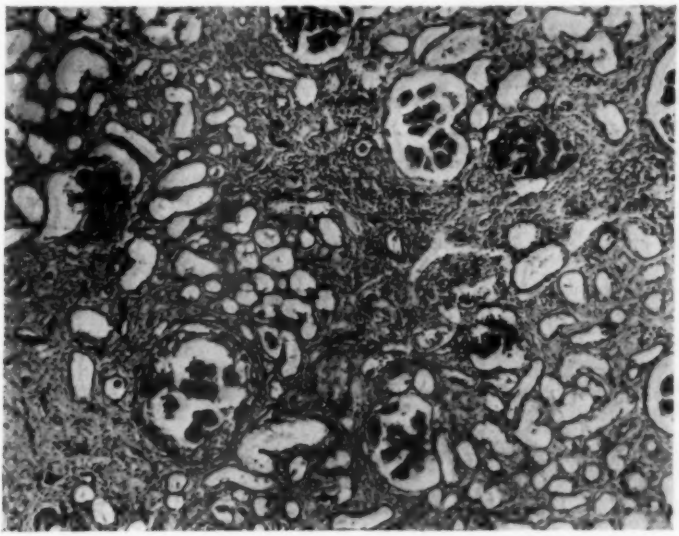


FIG. 2. SECTION OF CORTEX SHOWING EXTENSIVE INVOLVEMENT OF GLOMERULI WITH OLD CRESCENT FORMATION ADHESIONS AND MODERATE DEGREE OF INFILTRATION OF INTERSTITIAL TISSUES

albumin, with casts and red blood cells. These comparatively quiescent periods may be broken by acute exacerbations, accompanied by oedema, hypertension, and all the signs and symptoms encountered in cases of acute nephritis. As the disease continues, there is a tendency for the blood pressure to remain high permanently, for the oedema to subside, for changes in the eye-grounds to appear, for the anaemia to increase and for the measurable evidences of renal failure to become evident. In the later stages of the disease the picture may simulate

so nearly the condition seen in advanced arteriolar disease that a clinical differentiation is almost impossible.

In many instances indeed (Loehlein, Volhard and Fahr, Fishberg (34), Branch and Linder (35), and Baehr and Ritter (36)) the kidney at autopsy shows a combination of diffuse inflammatory lesions in the glomeruli and extensive changes in the arterioles or arteries; and there has been considerable discussion as to whether the clinical picture in the final stage of glomerular nephritis is not usually modified by the presence of arteriolar disease. By some (Fishberg) this is

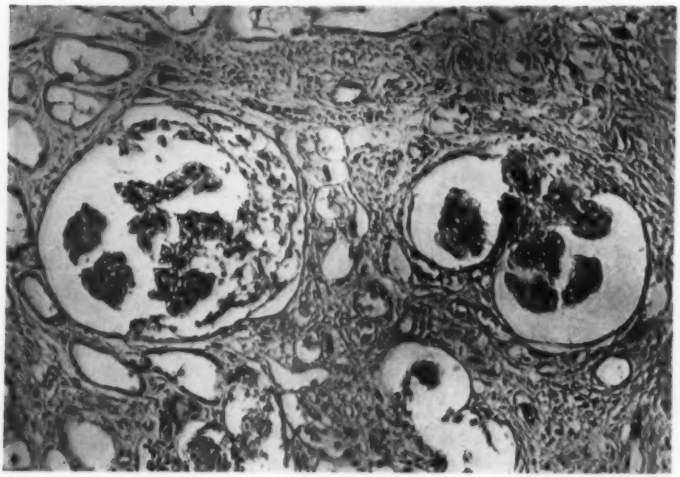


FIG. 3. MICROSCOPIC PICTURE OF TWO GLOMERULI

regarded as secondary to the glomerular nephritis, and explained as being dependent upon the mechanical increase in blood pressure caused by the glomerular nephritis; by others it is supposed that the diffuse glomerular nephritis and the arteriolar lesions may have a common etiology. Loehlein, as well as Volhard and Fahr, has pointed out that the arterial lesions are usually confined to the kidney; but Branch and Linder, as well as Fishberg, have described instances in which the arteriolar sclerosis is widespread throughout the body. It is, as a rule, only in the very chronic cases that the widespread arteriolar

lesions are found; and under these conditions the question must always arise whether the disease is primarily glomerular nephritis complicated by arteriolar sclerosis, or primarily arteriolar sclerosis complicated by a diffuse glomerular nephritis, a condition which Volhard and Fahr have described so fully. Such questions, however, can be answered only by the careful study of cases of glomerular nephritis, from the acute onset, through the various stages of development, to the terminal phase and death.

Dr. Bordley is now engaged in a careful correlation of the pathological lesions in our fatal cases with the course of the disease. The last case presented shows very definitely that the chronic glomerular nephritis may pass through the hypertensive stage to death without significant histological changes in the arterioles.

In conclusion, then, one may summarize the information that can be obtained about primary glomerular nephritis as follows. The disease occurs in two forms—the focal form and the diffuse form. The focal form occurs during acute infections, and in the embolic type is usually ascribed to the deposition of bacteria in the capillary loops of the glomeruli, where they lead to a necrosis, or to an inflammatory reaction. The diffuse form follows acute infections, proven to be due in such a large proportion of instances to haemolytic streptococci, that for the present it is justifiable to consider, at least one variety of acute glomerular nephritis, as a manifestation of streptococcic infection. In view of the great frequency of acute streptococcic infections, it must be considered as a rare manifestation. It cannot be proven that acute glomerular nephritis depends upon infection by a particular form ot streptococcus, or upon the invasion of the blood or the involvement of the kidney by streptococci. There is some evidence, however, which indicates that patients suffering from acute nephritis are abnormally susceptible to the products of the growth of haemolytic streptococci; and it seems possible that some altered reaction of the tissue, such as occurs in allergy, or some unusual antibody response to the infection is the determining factor in the development of acute glomerular nephritis in individual cases. Permanent recovery is apparently more common in children than in adults. We have no observations to explain the difference. In a small number of adults we have found that recovery has followed elimination of the infection and the

infecting organism, while progression of the disease has been coincidental with the persistence or the recurrence of haemolytic streptococcus infections. It further appears evident that there are instances of Bright's disease that run their entire course as progressive or recurrent diffuse inflammatory glomerulitis, without involvement of the renal arteries or arterioles, and with changes in the renal tubules that may be regarded as secondary to the glomerular lesion and to the diffuse inflammatory reaction of the interstitial tissue. As a working hypothesis, therefore, we would suggest that it may be possible to differentiate, as one form of Bright's disease, a primary and specific glomerular nephritis which is to be interpreted probably as a manifestation of streptococcus infections in individuals who may be allergic to the streptococcus or its products of growth, or who possess some other peculiar form of tissue response to a local streptococcic infection.

REFERENCES

(1) Bright, R.: Reports of Medical Cases, London, 1827; I, 67.

(2) Gull, W. W. and H. G. Sutton: On the Pathology of the Morbid State Commonly Called Chronic Bright's disease with Contracted Kidney. *Medico-Chir. Trans.*, 1872, **55**, 273.

(3) Loehlein, M.: (a) Über die entzündlichen Veränderungen der Glomeruli der menschlichen Nieren und ihre Bedeutung für die Nephritis. *Arbeit. aus dem Pathol. Inst. zu Leipzig*, Marchand, 1907, I; (b) Über Nephritis nach dem heutigen Stande der pathologisch-anatomischen Forschung. *Ergeb. der. Inn. Med. u. Kinderheilk.*, 1910, **5**, 411; (c) Über Schrumpfniere. *Beiträge z. Path. Anat. u. Allg. Path.*, 1917, **63**, 570.

(4) Jores: Über die Arteriosklerose der kleinen Organarterien. *Virch. Arch. f. Path. Anat.*, 1904, **178**, 367.

(5) Müller, F. (von): Morbus Brightii. *Verhandlung. der Deut. Path. Gesellschft.*, 1905, neunten Tag, 64.

(6) Bezeichnung und Begriffsbestimmung auf dem Gebiet der Nierenkrankheit, *Veröffenlich. aus dem Gebiet des Militär Sanitätswesens*, 1916, Hft. 65, 1.

(6) Volhard, F., u. Th. Fahr: Die Brightische Nierenkrankheiten, Berlin, 1914.

(7) Addis, Th.: A Clinical Classification of Bright's Disease. *Jour. Am. Med. Assn.*, **85**, 163, 1925.

(8) Loehlein, M.: Über hämorrhagische Nierenaffektionen bei chronisher ulzeröser Endocarditis. *Med. Klinik*, 1910, **6**, 375.

(9) Baehr, G.: Glomerular Lesions of Subacute Bacterial Endocarditis. *J. Exp. Med.*, 1912, **15**, 330; Glomerular Lesions of Subacute Bacterial Endocarditis. *Am. J. Med. Sc.*, 1912, **144**, 327.

(10) DENNY, E. R. AND B. M. BAKER: Varicella Complicated by Acute Nephritis. *Bull. Johns Hopkins Hosp.*, 1929, **44**, 261.

(11) BAEHR, G.: The Significance of the Embolic Glomerular Lesions of Subacute Streptococcus Endocarditis. *Arch. Int. Med.*, 1921, **27**, 262.

(12) LONGCOPE, W. T., O'BRIEN, D. P., MCGUIRE, J., HANSEN, O. C., AND E. R. DENNY: Relationship of Acute Infections to Glomerular Nephritis. *J. Clin. Inves.*, 1927, **5**, 7.

(13) OPHÜLS, W.: The Etiology and Development of Nephritis. *Jour. Am. Med. Assn.*, **69**, 1223, 1917.

(14) KUCZYNSKI, M. H.: Nephritisstudien. *Virch. Arch.*, 1920, **227**, 186.

(15) BELL, E. T., CLAWSON, B. J. AND T. B. HARTZELL: Experimental Glomerular Nephritis. *Am. J. Path.*, 1925, **1**, 247.

(16) KINSELLA, R. A. AND C. C. SHERBURN: Experimental Production of Streptococcus Endocarditis with Glomerular Nephritis. *Proc. Soc. Exp. Biol. and Med.*, 1922–23, **20**, 252.

(17) CLAWSON, B. J.: Experimental Focal Embolic Glomerular Nephritis in Rabbits. *Arch. Path.*, 1926, **1**, 911.

(18) DUVAL, C. W. AND R. J. HUBBARD: Experimental Glomerular Nephritis Induced in Rabbits with the Endotoxic Principle of Streptococcus Scarlatinae. *J. Exp. Med.*, 1926, **46**, 567.

(19) GRAY, J.: Causes and Sequences in Nephritis. *J. Path. and Bact.*, 1928, **31**, 191.

(20) RICH, A. R., BUMSTEAD, J. H. AND M. FROBISHER, JR.: Hemorrhagic Glomerular Lesions Produced by Filtrates of Streptococcus Viridans Cultures. *Proc. Soc. Exp. Biol. and Med.*, 1929, **26**, 397.

(21) TRASK, J. D. AND F. G. BLAKE: Observations on the Presence of a Toxic Substance in the Blood and Urine of Patients with Scarlet Fever. *J. Exp. Med.*, 1924, **40**, 381.

(22) SCHICK, B.: Die Nachkrankheiten des Scharlach. *Jahrb. f. Kinderheilk.*, 1907, **65**, 132.

(23) v. PIRQUET, C. E.: Allergy. *Arch. Int. Med.*, 1911, **7**, 259; 383.

(24) BRISTOL, L. D.: Scarlet Fever as a Reaction of Hypersensitiveness to Streptococcus Protein. *Am. J. Med. Sc.*, 1923, **166**, 853.

(25) DOCHEZ, A. R. AND F. A. STEVENS: Studies on the Biology of Streptococcus. *J. Exp. Med.*, 1927, **46**, 487.

(26) COOKE, J. V.: Scarlet Fever. *Am. J. Dis. of Child.*, 1927, **34**, 969; 129; **35**, 762, 772; 781; 784; 974; 983; 991.

(27) FRIEDEMANN, U. AND H. DEICHER: Weitere Klinische u. Experimentelle Untersuchungen über den Scharlach; Die Pathogenese der Scharlach Nephritis. *Ztschr. f. Klin. Med.*, 1928, **108**, 737.

(28) JAMES, R. F.: The Prognosis of Nephritis in Childhood. *Jour. Am. Med. Assn.*, **61**, 505, 1921.

(29) HANSBORG, H.: Untersuchungen über die Prognose der Scharlach Nephritis. *Acta Scand.*, 1924–25, **61**, 570.

(30) HUME, W. E. AND F. J. NATTRASS: The Late Effects of War Nephritis. *Quart. J. Med.*, 1927, **21**, 1.

(31) DEUTSCH, F.: Kriegsnephritikischickale. *Med. Klinik*, 1921, **17**, 1318.

(32) SIGURET, G.: *Arch. Méd.-Chir. de Province*, 1920, **16**, 845. (Quoted from Hume and Nattrass.)

(33) MAGNUS-ALSLEBEN, E.: Über die Folgezustände der Kriegsnephritis. *Deut. Med. Wchnschr.*, 1928, **54**, 1914.

(34) FISHBERG, A. M.: The Arteriolar Lesions of Glomerular Nephritis. *Arch. Int. Med.*, 1927, **40**, 80.

(35) BRANCH, A. AND LINDER, G. C.: The Association of Generalized Arteriolar Sclerosis with High Blood Pressure and Cardiac Hypertrophy in Chronic Nephritis. *J. Clin. Invest.*, 1926–27, III, 299.

(36) BAEHR, G. AND S. A. RITTER: The Arterial Supply of the Kidney in Nephritis. *Arch. Int. Med.*, 1929, **7**, 458.

THE EFFECT UPON HAEMOLYTIC STREPTOTOCCI OF CULTIVATING THEM IN IMMUNE AND NORMAL SERUM

ELEANOR A. BLISS[1] AND HAROLD L. AMOSS

From the Biological Division of the Department of Medicine, Johns Hopkins University and Hospital

In 1887 Metchnikoff (7) observed that anthrax bacilli greatly decreased in virulence after cultivation in homologous antiserum, and Charrin and Roger (2) demonstrated a similar effect with pneumococci, streptococci and *B. pyocyaneus*. The later investigations of Metchnikoff (8), Issaeff (5), and Sanarelli (9), however, seemed to indicate that this apparent loss of virulence was due to the continued presence of traces of the antiserum in the test material, since washed cultures of pneumococci which had been grown in immune serum were found to be even more pathogenic for mice than the original strain. Five or six other workers obtained similar results with intestinal bacteria, such as *B. typhosus* and the cholera spirillum.

Stryker (11), in 1916, repeating the experiments with pneumococci, confirmed the early work of Charrin and Roger. She observed that, after cultivation in immune serum, pneumococci had markedly decreased in virulence, and that this could not be explained by the presence of antiserum in the culture, as it persisted after 60 to 70 transplants in plain bouillon. She inferred that "some biologic change must have taken place in the organism, transforming it from the virulent to the avirulent form," an inference substantiated by the fact that these avirulent strains had also lost the power to form capsules and were easily phagocyted in normal serum. She had no explanation to offer for the difference in the results obtained with pneumococci and with typhoid bacilli but suggested that it might be due to the different kinds of antibodies produced in the two antisera.

In 1925, in an investigation (1) undertaken to show that a pure culture of pneumococcus was composed of strains possessed of varying

[1] Jacques Loeb Fellow in Medicine.

degrees of virulence, it was found that after four transplants in 10 per cent serum broth, the culture produced atypical colonies on blood-agar plates. The new colonies were granular, rough and grayish in colour. Cultures from them were like the original in that they were soluble in bile, that they fermented inulin and produced methaemoglobin in blood broth. But they were avirulent and their virulence could not be restored by animal passage.

Cowan (3), 1922, studying the variation of streptococci, selected for plating out those broth cultures which showed the most and the least even turbidity, and from the plates picked the most and the least typical colonies. After repeating this several times, she found that each of her strains yielded two distinct types. One type produced rough colonies and grew granularly in broth; the other formed smooth colonies and produced an even turbidity in broth. The rough strains, as a rule, grew in longer chains and showed a greater variation in size. They were less virulent for mice and rabbits. The haemolytic power of the two strains was equal.

On the other hand, Todd, (13, 14, 1927, 1928), in the course of an investigation of the virulence of haemolytic streptococci after cultivation in human blood and on agar, found that his avirulent organisms produced "glossy" colonies, while the virulent, or not completely attenuated cultures, formed "matt" colonies. He believed that his two types of colony were not the same as the "rough" and "smooth" colonies described by Cowan. He showed further that a strain of streptococcus, highly virulent for mice, became attenuated after cultivation in homologous convalescent serum. Later he and Lancefield (15) demonstrated that the "matt" and "glossy" cultures produced equally potent toxins, and they concluded that there was no relationship between virulence and toxigenicity.

Most recently Eagles (4), 1928, found that with one of his strains smooth colonies were formed by the attenuated organisms and rough by the virulent, while with the other strain the reverse was true, and he held, therefore, that colony appearance was not a "reliable indication of virulence in haemolytic streptococci." At the same time he noted among his colonies five different degrees of roughness which corresponded to different degrees of pathogenicity.

EXPERIMENT 1

Method

Two virulent, toxigenic strains, B and P, of erysipelas streptococci were transplanted daily for twenty-one days in 1 part of immune serum to 10 parts of beef-infusion broth. As a control they were cultivated in normal horse-serum broth. Later the number of subcultures was increased to 40 without altering the effects observed after 21 transplants.

Results

Growth. After 21 transplants there were several differences between the immune and the normal serum series. The most noticeable difference was in the appearance of the broth cultures. The immune-serum strain, after the first transplant, grew smoothly in broth and remained in suspension. The normal serum strain, like the original culture, was granular in broth, or if growth appeared diffuse at the end of eighteen hours' incubation, it soon settled out at room temperature as a coarse precipitate.

Morphology. There was but slight difference in the microscopic appearances of the organisms. The normal serum strains grew in comparatively long chains, the immune in short chains of large cocci; both varied greatly in the length of the chains and in the size of the cocci and both produced involution forms.

pH. The hydrogen-ion concentration in plain beef broth at the end of 24 hours was the same with both strains.

Haemolysis. The same degree of haemolysis was observed in the two series in erythrocyte suspensions and on blood-agar plates.

Fermentation. The fermentation reactions of the two series were identical.

Pathogenicity. There was a marked difference in the pathogenicity of the two strains. Both of the immune-serum strains showed a great loss of virulence and of power to produce filtrable toxic substances, while the normal-serum strains retained their original potency.

Skin reactions in rabbits were used as the measure of the virulence of the strains. This is a better test than the determination of the lethal dose in rabbits by intravenous injection, as these animals vary

greatly in their susceptibility to streptococci. Several intracutaneous injections can be made at one time in a single rabbit.

Test cultures were grown in beef-infusion broth. An attempt was made to equalize the number of organisms per cubic centimeter in the cultures used on a given day by bringing them to the same turbidity with a Gates suspensiometer, or by counting the organisms in a bacterial counting-chamber and making suitable dilutions. There are obvious objections to both methods.

Pathogenicity

Rabbit 707, 11–27–26, was injected intracutaneously with 0.2 cc. of the following cultures grown in broth and counted in a bacterial counting chamber:

Strain B_o (not grown in either immune or normal serum).
Strain B_{21}Im. (21 subcultures in immune serum).
Strain B_{21}N. (21 subcultures in normal serum).
Reactions: 11–28–26.

B_o: reddening and oedema with a small patch of skin necrosis, 4.0 × 1.0 cm. in area.

B_{21} Im: small papule, 0.3 cm. in diameter with a small zone of faint erythema below it.

B_{21} N: Two small areas of reddening and oedema, the upper one measuring 1 cm.², the lower 0.5 × 1 cm., connected by a band of faint reddening. The whole lesion measured 3 × 1.2 cm.

Rabbit 456, 2–18–27, was injected intracutaneously with 0.2 cc. of the following equalized suspensions from blood-agar slant cultures.

Strain P_o (not grown in either immune or normal serum).
Strain P_{40} Im. (40 subcultures in immune serum).
Strain P_{40} N. (40 subcultures in normal serum).
Reactions: 2–19–27.

P_o: reddening and oedema with a small patch of skin necrosis, 5.5 × 1.2 cm.

P_{40} Im: reddening and oedema with a small patch of skin necrosis, 3.3 × 1.4 cm.

P_{40} N: reddening and oedema with a small patch of skin necrosis, 3.6 × 2 cm.

2–20–27. Measurements: P_o: 5 × 3 cm.; P_{40} Im: 3.5 × 1.6 cm.; $P_{40}N$: 4.5 × 3.5 cm.

Rabbit 822, 2–18–27, was injected intracutaneously with B cultures prepared in the same manner as those used in rabbit 456:

Strain B_o; strain $B_{40}Im$; strain $B_{40}N$.

Reactions: 2–19–27.

B_o, oedema, slight reddening with skin necrosis and haemorrhage, 2.5 × 1.5 cm.

$B_{40}Im$, reddening and oedema with tiny spot of necrosis at point of inoculation, 4.5 × 1.6 cm.

$B_{40}N$, slight oedema with red margin, extensive necrosis and haemorrhage, 7.5 × 3 cm.

2–20–27. Measurements: B_o 7.5 × 5 cm.; $B_{40}Im$, 4.8 × 1.8 cm.; $B_{40}N$, 12 × 3.5 cm.

TABLE I

Skin reactions to filtrates of streptococcus strains grown in immune and normal serum

PATIENT	B			P		
	No serum	Immune	Normal	No serum	Immune	Normal
Fink*	2.5 × 2 cm.	2 cm.²	2.5 × 2 cm.	4 × 3.5 cm.	3 × 2 cm.	3 cm.²
Stev	1.7 × 1 cm.	0.5 cm.²	1.2 cm.²		1.3 × 1 cm.	3 × 2.5 cm.
Welc	2.6 × 2 cm.	0.5 cm.²	2.5 × 2 cm.		1 cm.²	3 × 2.3 cm.
Stin		0.2 cm.²	2 × 1.5 cm.		1.7 × 1.3 cm.	2.7 cm.²
Kern	2.8 × 2.5 cm.	2 cm.²	2.5 × 2.3 cm.		2.5 × 3 cm.	4 cm.²

* Received filtrates from B_{21} and P_{21}; others from B_{40} and P_{40}.

Toxigenicity. A toxic filtrate (Seitz) of each series of the two strains was prepared from twenty-four-hour Stickel and Meyer (10) tryptic digest broth cultures. Tests were made by intracutaneous injections of 0.1 cc. of 1 to 100 dilutions of the filtrates in the forearms of susceptible persons. Reactions are shown in Table I. In three of the patients the reactions to the immune-serum strain filtrates were much less pronounced than to the normal-serum strain filtrates. Two of the patients did not show a great difference in reactivity, but it may be stated that the toxigenicity of a strain of streptococcus is lowered by cultivation in immune serum.

Immunological properties. Agglutination reactions were more satisfactory with the immune serum strains because of their diffuse growth

in broth. They agglutinated in a higher dilution of erysipelas horse antitoxin than the normal-serum strain, 1 to 1280 as compared to 1 to 640. But one of them, B_{21}, also agglutinated in a 1 to 320 dilution of scarlatinal antitoxin, implying a loss of specificity on the part of this strain. To test this further, rabbits were immunized against one immune and one normal-serum strain derived from the same original culture (B). Both sera agglutinated both the immune and the normal strains in a dilution of 1 to 40,960.

A type specific protein substance was prepared from each strain by Lancefield's (6) method of extracting the bacteria with HCl. Both of the extracts caused precipitation in the two high-titred rabbit sera mentioned above. They did not cause precipitation in a heterologous streptococcus immune serum which was known to contain precipitins. Nor did another heterologous streptococcus antigen result in precipitation in these sera, although the strain agglutinated in a very high titre with one of them.

Except for a slight loss of agglutinin specificity on the part of the immune serum strain, the antigenic properties of the immune and normal serum strains may be summed up as identical.

Colony production. Two types of colonies were observed on blood-agar plates from both series, smooth, white, glistening colonies and dull, brownish colonies with a small mound at the centre which gave them a rough appearance. On plates from both series the smooth colonies predominated. There was, however, a larger proportion of rough colonies on the normal serum strain plates, 8 to 10 per cent, than on the immune, 2 to 4 per cent. There were no detectable differences in the cultures made from the rough and smooth colonies from a given strain, either in their growth in broth, haemolytic power or pathogenicity.

Pathogenicity. The B and P cultures of the different strains were mixed in equal proportions and 0.2 cc. of the mixtures injected intracutaneously in rabbits 705 and 817. The reactions were as follows:

B & P:

From immune serum	Rabbit 705	Rabbit 817
a. Smooth colony.	Tiny papule, no erythema.	Tiny papule, faint erythema 2.5 × 1.0 cm.
b. Rough colony.	Tiny papule, no erythema.	Tiny papule, faint erythema 1.7 × 1.0 cm.

From normal serum	Rabbit 705	Rabbit 817
a. Smooth colony.	Slight oedema, no erythema 3.8 × 2.0 cm.	Oedema, erythema and necrosis with haemorrhage 1.8 cm.²
b. Rough colony.	Slight oedema, no erythema 2.8 × 1.5 cm.	Oedema, erythema and necrosis with haemorrhage 2.5 × 1.8 cm.
Not grown in serum	Slight oedema, no erythema 3.0 × 1.8 cm.	Oedema, erythema and necrosis with haemorrhage 2.7 × 1.5 cm.

EXPERIMENT 2

Method

The method was the same as in experiment 1 except that strain B only was used.

Results

The growth was smooth in immune serum after the second transplant. In normal serum it remained granular until the nineteenth subculture when it became diffuse. However, when it was centrifuged and resuspended, clumping again occurred. As in the first experiment, the haemolytic power and the fermentation reactions of the two strains were the same. The immune serum strain again showed a loss of pathogenicity and toxigenicity.

Pathogenicity. Rabbit 1007, 5–12–27, was injected intracutaneously with 0.2 cc. of the following 24-hour broth cultures:

(1) B_{17}Im. (17 transplants in immune serum).

(2) B_{17}N. (17 transplants in normal serum).

Reactions: 5–13–27:

B_{17}Im. Oedema and erythema 2.3 × 1.7 cm. with small area of skin necrosis.

B_{17}N. Marked necrosis bounded by red indurated edge. Whole lesion is 3.5 × 1.5 cm.

Toxigenicity. Miss Z. was injected intracutaneously in the left forearm with 0.1 cc. of 1 to 100 dilutions of the following filtrates:

(1) B_0 (not cultivated in serum).

(2) B_{20}Im. (20 transplants in immune serum).

(3) B_{20}N. (20 transplants in normal serum).

Reactions:

B_0 Erythema and oedema 3.0 × 3.5 cm.

B_{20}Im. Moderate erythema, very slight oedema 1.2 × 1.4 cm.

B_{20}N. Marked erythema and oedema 3.0 × 3.3 cm.

DISCUSSION

In these experiments the pathogenicity for rabbits of two strains of *Streptococcus erysipelatis* was found to be diminished by cultivation in homologous immune serum. This is in agreement with the results of Stryker and of Amoss for pneumococci and of Todd for streptococci. The results obtained here differ from those of Todd, Cowan and Eagles, in respect to the relative virulence of the rough and smooth colony strains. It will be recalled that Todd found the rough strains to be virulent for mice; Cowan found the reverse for rabbits and mice and Eagles observed that the respective virulence of the rough and smooth types varied with different cultures. In the present experiments it has been shown that, although there was a slightly larger proportion of rough colonies on a plate from a virulent culture than on one from an attenuated culture, the rough and smooth strains from one culture were equally pathogenic for rabbits. Given a virulent culture, the smooth as well as the rough derivatives were virulent for rabbits.

In discussing the possible reasons for this diversity of findings, the variations in the media employed may be disregarded, as each worker observed the distinct differences between the rough and the smooth colonies. The fact that rabbits were used here instead of mice in the virulence tests might account for the difference in the results obtained here and by other workers were it not that Cowan used both animals and that Todd and Eagles, both of whom used mice, disagree in their results. There is also the possibility that the rough and smooth strains isolated in the present study were not completely dissociated. In that case, however, one would not expect so pronounced a difference in colony formation as was noted.

There must be still another explanation of the varied results. It appears that the roughness or smoothness of a colony is a biological property of the organism rather than a temporary reaction to environment, since Todd, Cowan and Eagles all showed that the two types were dissimilar and since similar observations have been made in the case of several other species of bacteria. There remains the possibility

that, besides the two kinds of haemolytic streptococcus culture described by Eagles, in one of which the rough strains are virulent and in the other the smooth, there is a third in which there is no difference between the two derivatives. One concludes with him that colony formation is a poor criterion of virulence.

SUMMARY

1. Two strains of erysipelas streptococci were found, after cultivation in homologous immune serum, to have deteriorated in toxigenicity and in pathogenicity for rabbits, while the same strains cultivated in normal horse serum maintained their original potency.

2. In broth, the normal-serum strain as well as the original culture produced a coarse precipitate, while the immune-serum strain grew diffusely.

3. The other biological properties, such as fermentation reactions, haemolytic power and colony formation, of the two strains remained unchanged.

4. Two kinds of colonies, rough and smooth, were observed on plates from the immune-serum series, the normal-serum series and the original cultures.

5. There was no difference in the pathogenicity for rabbits of a rough and a smooth colony strain from a given culture. Those from the normal serum were equally virulent, while those from the immune serum were equally attenuated.

REFERENCES

(1) Amoss, H. L.: The composite nature of a pure culture of a virulent pneumococcus. *J. Exp. Med.*, 1925, xli, 649–662.

(2) Charrin et Roger: Atténuation des virus dans le sang des animaux vaccinés. *Compt. rend. Soc. Biol.*, 1892, iv, 620, 924.

(3) Cowan, Mary L.: Variation phenomena in streptococci, with special reference to colony formation, haemolysin production and virulence. *Brit. J. Exp. Path.*, 1922, iii, 187.

(4) Eagles, G. Hardy: Colony variants in haemolytic streptococci. *Ibid.*, 1928, ix, 330.

(5) Issaeff, B.: Contribution à l'étude de l' immunité acquise contre le pneumococque. *Ann. de l'Inst. Pasteur*, 1893, vii, 260.

(6) Lancefield, Rebecca C.: The antigenic complex of streptococcus haemolyticus. *J. Exp. Med.*, 1928, xlvii, 91.

(7) METCHNIKOFF, E.: Sur l'atténuation des bactéridies charboneuses dans le sang des moutons réfractaires. *Ann. de l'Inst. Pasteur*, 1887, i, 42.

(8) METCHNIKOFF, E.: Études sur l'immunité. *Ann. de l'Inst. Pasteur*, 1892, vi, 297.

(9) SANARELLI: Moyens de défense de l'organisme contre les microbes après vaccination et dans la guérison. *Ann. de l'Inst. Pasteur*, 1893, vii, 225.

(10) STICKEL AND MEYER: Peptic and tryptic digestic products as inexpensive culture media for routine bacteriological work. *J. Inf. Dis.*, 1918, xxiii, 68.

(11) STRYKER, L. M.: Variations in the pneumococcus induced by growth in immune serum. *J. Exp. Med.*, 1916, xxiv, 49.

(12) TODD, E. W.: Observations on the virulence of haemolytic streptococci. *Brit. J. Exp. Path.*, 1927, viii, 289.

(13) TODD, E. W.: The influence of the sera obtained from cases of streptococcal septicaemia on the virulence of the homologous cocci. *Loc. cit.*, p. 361.

(14) TODD, E. W.: Further observations on the virulence of haemolytic streptococci, with special reference to the morphology of the colonies. *Brit. J. Exp. Path.*, 1928, ix, 1.

(15) TODD, E. W., AND LANCEFIELD, REBECCA C.: Variants of haemolytic streptococci; their relation to type-specific substance, virulence and toxin. *J. Exp. Med.*, 1928, xlviii, 751.

A STUDY OF REFLEXES IN THE DEAFFERENTED LEG OF THE CAT AND THEIR RELATION TO TONUS

WILBUR L. SPRONG

From the Sub-Department of Neurology, the Johns Hopkins University

INTRODUCTION

Skeletal muscles deafferented by cutting dorsal nerve roots have been frequently studied. However, while some observers have concluded that such muscles are atonic (Sherrington, 1909, and Coman, 1928), others have believed they are tonic or even hypertonic (Ranson, 1928). Naturally, with such discordant experimental results, quite different rôles have been attributed to the dorsal roots in the maintenance of tonus. The reasons for these discrepancies may lie in the technique employed, but are perhaps more often to be found in the mode of observation, and in the interpretation of what was observed.

A difficulty immediately encountered in the study of tonus is the prevailing lack of uniformity in the use of the term. Various theories that have been proposed reveal at once that they are based on different concepts of what the objective phenomenon really is. In as much as investigators of tonus have not been looking for the same thing, diverse conclusions are not surprising. Sherrington's definition, "postural contraction" implies an essential function of tonus, giving at once significance to its distribution among muscles, its shifts and alterations, and its close relation to the proprioceptive system. It is, therefore, the most illuminating definition that has been presented, and yet it is not a concept sufficiently inclusive and exclusive to enable different observers uniformly to recognize the presence or absence of tonus in a limb.

The problem is further complicated by the fact that deafferented muscles contract freely in response to numerous extrinsic afferent impulses. Tonus, or postural contraction, may thus be readily simulated, particularly when the animal is observed in a position in which it is at all active, in which case much extrinsic reflex influence may be introduced.

In a non-decerebrated animal, the opposite normal leg offers no adequate control with which to compare the deafferented leg. If the normal leg is examined by passive manipulation, new afferent impulses, principally cutaneous, cause the manipulations to be resisted by active withdrawing movements, which obscure the resting tonus. The deafferented extremity swings passively and hangs to a lower level than the normal one of the other side; its tonus is obviously diminished, but these criteria do not prove that it is entirely atonic.

It is not proposed to discuss the vast literature dealing with the problems of muscle tonus, but some of the observations, most pertinent to the present investigation, will be considered. A thorough review of the subject is available in Fulton's monograph (Fulton, 1926).

Sherrington (1909) discussed in detail the differences between the normal and the deafferented vastocrureus muscle in the decerebrate cat. The normal muscle always developed decerebrate rigidity, gave exaggerated knee jerks, and exhibited prominent lengthening and shortening reactions, whereas the deafferented muscle showed no trace of decrebrate rigidity, total absence of knee jerks, no shortening reaction, and no true lengthening reaction. In short, the deafferented muscle showed none of the phenomena which Sherrington believed characteristic of the tonic state. Moreover, none of these losses occurred when every other muscle of both legs was severed from its nervous connections. Hence, it was logically concluded that these properties depend upon the integrity of afferent fibers from the muscle itself, and from that muscle only. From these findings and those of related experiments, Sherrington formulated the theory that muscle tonus is a proprioceptive reflex, the afferent portion of which consists exclusively of afferent fibers from the muscle itself.

In this vastocrureus muscle, devoid of its afferent innervation, contractions were elicited reflexly by stimulation of extrinsic afferent nerves, but these contractions reached a sudden maximum, and then gave way to abrupt relaxation in contrast to the slow subsidence in the normal tonic muscle. In certain cases, a brief delay in relaxation, after the stimulus was withdrawn, could be detected, and was shown to be due to an "after-discharge phenomenon" in the extrinsic nerve stimulated. This was clearly differentiated from the sustained contraction of the normal muscle. In this way, atonus may be noted not

only in the resting muscle, or limb, but also in the midst of active movements, by a conspicuous lack of the normal smooth transitions between different degrees of tension. Indeed, this is one of the most prominent manifestations of atonus in the kind of preparations used in the present investigation.

Ranson (1928a) agreed with Sherrington that the dorsal roots play an indispensable rôle in muscle tonus, but questioned that the ventral roots convey the efferent impusles involved. He regarded tonic contraction as a phenomenon qualitatively different from other muscular contraction, involving a different metabolism, dependent upon impulses from some source not yet determined. That it is those properties derived from reflex shortening and lengthening reactions, aroused by proprioceptive impulses, was considered to be an inadequate view. A number of facts were enumerated which would seem to support the postulate of Frank (1921) that the dorsal roots include fibers which conduct special tonic impulses antidromically to the muscles. He included, in this paper, studies based upon a series of cats with one hind limb deafferented by cutting the dorsal roots of the spinal nerves intradurally. It was found that, after an initial period of flaccidity lasting about twenty-four hours, there was an increased resistance to passive flexion, and an over-action of the extensor and adductor muscles, quite similar to the spasticity found in upper motor neurone lesions. This hypertonus lasted usually two or three weeks. The cats had difficulty in flexing the leg, due to the over-extension. The crossed extension reflex in response to flexion of the opposite leg was regularly observed. Decerebrate rigidity of a tremulous oscillatory type developed in the deafferented leg but plasticity was entirely absent.

In four of Ranson's cats, not only were the dorsal roots sectioned but the ganglia were removed. These animals, however, showed none of the evidences of hypertonus so common in the rest of the series; there was no increased resistance to passive flexion, and no overaction of the extensor muscles. In certain cats, a contracture-like condition of the deafferented muscle developed which was said to resemble decerebrate rigidity. However, it remained after the animal was thoroughly anaesthetized or even killed with ether, indicating that it was not maintained by nervous influence.

In a more recent paper (Ranson, 1928b), it was found that local

tetanus, produced by injection of tetanus toxin, led in time to a contracture not unlike the one described above. This condition could be produced much more readily in the deafferented than in the normal leg. It developed, likewise, after complete removal of the dorsal ganglia. The tetanus was apparently regarded as essentially the same phenomenon as tonus, and it was concluded that the findings failed to support either his own or Sherrington's theory.

In connection with the theory of antidromic conduction over the dorsal roots of the impulses concerned in muscle tonus, a series of experiments by Coman (1926) seem to apply in a very crucial way. While these experiments were designed to test the hypothesis that sympathetic fibers supply muscles with tonic impulses, they are equally applicable to the antidromic theory. The ventral roots of the nerves to the fore leg in the cat were cut, leaving the dorsal roots intact. Thus, preparations were obtained in which the postulated antidromic arc was wholly intact. Yet the leg was not only motionless, but utterly devoid of tonus. In a later series of experiments, the results of which appeared only in an abstract, Coman (1928) reported that in legs deafferented with minimal cord injury, absolute atonus resulted. He regarded trauma to the cord as the factor responsible for the existence of hypertonus. Ranson, on the other hand, attributed the flaccidity so frequently observed and which in most of his animals was only transient, to undue cord injury.

In Fulton's summary of the current views of muscle tonus, (Fulton, 1926) a thorough presentation of the proprioceptive reflex theory of Sherrington in the light of subsequent anatomical, metabolic, and electromyographic studies was given. He concluded that this theory still offers the most adequate explanation of all available facts.

The varied postures of an animal at rest, or in motion, all involve intricate patterns of tonic distribution, produced and maintained by the integration of many reflexes arising from different sources. Of the components acting in this complex process, the Magnus de Kleyn neck and labyrinthine reflexes play a prominent rôle and have been particularly well analyzed (Magnus, 1924). Not only do shifts in the position of the head, or accelerations of the animal in space, arouse transient impulses from these sources, but in static postures (*e.g.*, the neck held to one side), the final common path neurones are subjected to a con-

tinuous flow of impulses. The question arises, can these extrinsic impulses, alone, acting upon ventral horn cells maintain true postural contraction in a muscle, or are they effective only when superimposed upon the intact local proprioceptive reflex arc? Strictly interpreted, the proprioceptive reflex theory would imply only the latter possibility, but so far as the writer has been able to determine, neither Sherrington nor Magnus have dealt explicitly with this question.

The contradictory results of recent investigations seem to justify further objective descriptions of the altered properties of a deafferented leg, and careful analysis of the exact deficiencies in muscular function that may be referred to removal of the intrinsic afferent innervation.

METHODS

A series of operations was performed on adult cats, using aseptic technique and the following general procedure: For anesthetic, a regulated mixture of ether and air was administered through a catheter inserted into the trachea. The spines and laminae of the lower five lumbar vertebrae and upper sacrum were exposed through a longitudinal dorsal mid-line incision, the attached muscles being bluntly separated from the spines with a periosteal elevator. Minimal muscle bleeding was thus incurred. The spines were cut away with bone forceps and the laminae removed from both sides with rongeurs. No large arteries were encountered and the diffuse bleeding either ceased spontaneously, or was controlled by bits of muscle. With small scissors a longitudinal midline incision was made in the dura, exposing the cord throughout the proper segments, and all of the dorsal roots on one side, from the third lumbar to the third sacral nerves inclusive, were sectioned. In some cases, the operation was bilateral, as discussed below. After the roots were sectioned, the proximal portions were gently pushed up over the cord and a systematic search made for any roots that had been missed. The completeness of the operation can be easily and accurately verified in this way. The dural incision was not closed. The muscles were pulled together over the cord, the fascia reunited by continuous sutures, and the skin incision closed by subcutaneous sutures of silk.

A few animals that became infected were sacrificed and not included in the series studied. Each cat was autopsied, immediately after

death, in order to verify again the completeness and accuracy of the operation, and to investigate the condition of the cord.

The present study is based upon twenty adult cats that may be divided into three groups: (1) Eleven cats in which one hind leg was deafferented by cutting the dorsal roots from the third lumbar to the third sacral segments inclusive. (2) Four cats in which both hind legs were deafferented. (3) Five cats in which one hind limb was deafferented and the opposite leg completely denervated by cutting, intradurally, both dorsal and ventral roots from the third lumbar to third sacral segments inclusive.

Two animals in which one leg had been deafferented with the usual care to avoid trauma to the spinal cord, developed a peculiar rigidity of the deafferented muscles, whereas in all of the others the muscles appeared atonic. Since cord injury is often regarded as a cause of aberrant results, in three animals the dorsal roots on one side were sectioned and the cord deliberately subjected to slight definite trauma in the form of tiny shallow cuts along the dorsal and lateral funiculi on the side of the operation. It seemed certain that the injury here would be appreciably greater than the accidental or unavoidable injuries which had occurred in any of the other experiments.

In cats with one leg deafferented and the opposite one denervated, a preparation was obtained with a control limb which could safely be assumed to represent absolute atonus. By deafferenting both hind legs, the usual crossed extension reflex was eliminated and the rôle of afferent impulses from the fore legs, the neck, and the labryrinths could be studied, uncomplicated by those from the other hind leg. At the same time, this gave opportunity to study alternate stepping movements in the absence of mutual interaction of the hind limbs through their afferent stimuli.

Three cats which had survived the operation for 69, 76, and 77 days, were decerebrated by sectioning the brain at the intercollicular level by the trephine method. In all of the animals with unilateral operation, the cord was fixed in formalin and sections prepared with both hematoxylin and eosin, and Weigert stains (the latter by the method of Spielmeyer), in order to study further the amount of cord injury.

OBSERVATIONS

1. Preparations with one hind leg deafferented

Flaccidity of the deafferented limb at rest; the sources and phasic character of its reflexes. In cats in which the dorsal roots to one hind leg were severed, the experimental leg began active movements before recovery from the ether anaesthetic was complete. As the animal became active, there was usually a period of general excitement in which the head was thrown back and all four legs executed rhythmic, often rapid, running movements. The deafferented leg participated in this activity, showing unimpaired coördination with the other three legs, but the force and extent of each excursion were diminished.

The crossed extension reflex was clearly demonstrated in the deafferented leg in every animal, usually appearing within twenty-four hours after the operation, and reaching its maximum after two more days. The response was elicited by pinching the toe of the opposite hind leg, causing an active withdrawal of the latter. It could be shown in other ways. If the cat was held by the neck and was lowered so that the control hind leg touched the edge of a table, the deafferented leg was at once extended. Placing the cat in a sitting position with the fore legs on the floor caused the deafferented leg to be sharply extended; the opposite extremity being flexed as is normal in assuming this position. The deafferented leg, lacking the usual tactile stimuli for this response and receiving from the opposite side the adequate stimulus for a crossed extension, was extended.

It has already been mentioned that immediately following the operation, movements of the deafferented leg occurred, which were coördinated with the movements of the other extremities, and that within a short time, a crossed extension reflex could be elicited on stimulation of the opposite limb. It is now important to gauge the condition of the musculature of the deafferented leg when the cat was quiet, so that no extraneous stimuli were acting on the extremity. If the cat was held by the neck, the leg operated upon hung at a lower level than its fellow of the opposite side, which was usually well flexed, indicating a decreased tonus in the muscles deprived of their afferent connections with the central nervous system. The best observations concerning the resting condition of the deafferented muscles were

obtained when the cat was placed upon its side, and coaxed into an attitude of complete relaxation. In such a quiet cat the normal legs were relatively flaccid and yet the deafferented leg offered even less resistance to passive flexion and extension. Indeed, there was no evidence of tonus in the deafferented extremity in contrast to a certain residual tonus in normal muscles. After killing the cat with ether, the deafferented leg underwent no further relaxation. This strongly indicates that it had been not only hypotonic, but atonic.

It is already clear that in such a leg, although many movements do occur, there is no enduring tonus; this study deals particularly with the source and types of stimuli that may produce responses. A crossed extension reflex was elicited on stimulation of the opposite extremity. Impulses arising from the vestibular apparatus and from the deep neck musculature also called forth responses. Thus, if the cat, blindfolded and held by the neck, was allowed to drop a short distance, an extensor thrust was perceptible in the deafferented leg. When the head was sharply flexed on the body, a transient, increased extensor resistance was again present in the leg which had been operated upon. Sharply turning, or rotating, the head toward the side of the operation produced a similar extension. It is important to remember that these responses were transient, and that the musculature became flaccid immediately, when the stimulus ceased.

Movements, which were apparently purposeful, were executed by the deafferented leg. If the cat was suspended by the neck, attempts were made to reach and push aside the hand that held it. In these efforts, the injured extremity was repeatedly flexed to the level of the animal's neck, although in a noticeably more awkward, sweeping fashion than any of the other legs. Later, it was found that holding the other limbs and the head immobile prevented any response in the deafferented extremity, even though the cat became exceedingly angry and excited. Numerous consistent observations strongly suggest that any muscle contraction in the deafferent leg is impossible, save in conjunction with contractions of extrinsic muscles. On this basis, it would not be surprising to find that the more highly integrated impulses from the brain, involved in purposeful movements, can lead to a localized response only when the local reflex arcs are intact. Purposefulness, of course, is subjective, and can only be inferred from such objective observations.

When the cat was lying on its back, it was found that slight contractions of the deafferented muscles would accompany a sudden vigorous general contraction of the body musculature, although the head and the other legs were not permitted to move. Stimuli from the body musculature are able to exert an influence upon the deafferented leg, producing movements of the flexors or extensors.

While held in any position, excitement of the cat led to more or less of these overflow responses in the deafferented leg, depending upon the freedom of the other parts to move. Therefore, mere resistance of the limb to passive manipulation may be a misleading criterion for tonus unless precautions are taken to eliminate extraneous influences. Nearly all proprioceptive impulses may be eliminated by preventing movement of the animal in space, fixing the neck in relation to the body, and immobilizing the other limbs. Under these conditions the deafferented leg was found to be completely motionless and atonic, except during a violent struggle when imposed restraints were slightly overcome and the trunk musculature contracted vigorously. Then random phasic movements of a sudden and unsustained character appeared.

With these data concerning the types of impulses that give responses in deafferented muscles, the more complex activity in which the operated leg participated becomes more comprehensible. Walking usually commenced within twenty-four hours, in three cases within two hours, after the operation. On the following morning, however, and continuing for one or two days, the cat usually showed signs of the usual post-operative discomfort, and attempted to move but little. After a week, in the majority of cases, the animal could walk freely and even run. In progression, the movements of the deafferented leg were of special interest, since the deficiencies in function brought out in this process, if properly analyzed, doubtless would indicate precisely those properties which the leg muscles derive exclusively from their intrinsic afferent innervation. In stepping, the injured leg was directed against gravity only in as much as, between steps, it fell passively into the proper position. Some steps were executed almost normally, except that the abrupt relaxation of the leg that had been operated upon, following each extensor thrust, and the consequent hastening of the normal limb with the next step, produced an obvious limping

gait. If a proper rapidity was reached, the limp disappeared. If the limb happened to be pointing backward, more than the usual flexion force would, of course, be required to flex it properly between steps. A normal leg promptly accommodates itself to such a situation by stronger flexion. The deafferented leg, however, devoid of the local afferents upon which the primary influence of the disturbed position would be exerted, responded only with inadequate flexion force, and was dragged along, not participating, apparently, in progression. Upon palpation, however, the usual alternate flexion-extension contractions were found present, but isometric. Again, if the deafferented extremity happened to be in extreme abduction, stepping movements were made with no corrections. Absence of postural contraction was evident in the toes which remained always inadequately extended, so that, in stepping, the weight of the animal was often placed upon the dorsum of the digits instead of the sole of the foot.

Atonus of the deafferented pelvic musculature. In each cat in which dorsal roots were sectioned on one side only, there was a lateral deviation of the pelvis and lumbo-sacral spine toward the normal side. The animal was therefore inclined to fall to the side of the operation and it was only gradually that it learned to overcome this tendency. As the cat fell, the deafferented leg gave a strong extensor thrust. Ranson (1928) regarded tilting of the pelvis secondary to an adduction of the injured leg, and believed that an overaction of the extensors prevented the leg from functioning properly. From observation of the present series of animals, it seemed more probable that, with the unilateral atonus of the musculature of the lower spine and pelvic girdle, the lateral deviation was produced by action of the normal antagonistic muscles. There was no evidence of an overaction of the adductor muscles of the thigh, and it seemed certain that the adducted position of the operated limb was due to this tilting of the pelvis, particularly since the opposite normal leg was in an equivalent position of abduction from the midline of the body. Here, absence of tonus manifested itself again, just as might be expected, in a disturbance of posture; in this case, that of the pelvis. The evidence for this view seems conclusive, in the cases discussed below, in which dorsal roots were cut on each side, and there was no pelvic deviation nor adduction of either limb.

Contracture of deafferented muscles in animals with undue cord injury. Two of eight cats, in which one hind leg had been deafferented with the usual precautions against cord injury, developed in that leg a condition which seemed in striking contrast to the flaccidity shown by all of the others. These individuals recovered quite promptly from the anaesthetic, and developed the usual crossed extension and reflex stepping movements. However, they were somewhat slow in beginning to walk; both hind legs were dragged. After eight days in one, and fifteen days in the other, a resistance to passive manipulation was noted. The leg became increasingly stiff from day to day; in no position was it relaxed. This condition was described by Ranson in some of his experiments. In agreement with his findings, the deafferented legs of these animals failed to lose their rigidity after complete ether narcosis and death. In these two animals there was a loss of bladder control. The others were free from this disturbance.

Since similar results in such experiments have frequently been blamed upon injury to the cord, three cats were deliberately subjected to cord trauma, in addition to the usual operation as discussed above. In the first of these, after twenty-four hours, the crossed extension reflex appeared, and stepping movements were feebly participated in by the operated leg. Incontinence of urine appeared early, the exact time not being noted. Four days after operation, the contracture-like stiffness was first observed. The leg was not fixed in extreme extension, but in a relatively neutral position between extension and flexion. This condition showed a gradual increase until the animal died twenty-four days after operation. The other two preparations of this kind gave a similar picture, but showed signs of greater injury. They did not develop the crossed extension reflex until five and six days, respectively, after operation. There was continuous urinary incontinence; ulcers formed in the region of the buttocks, the results, perhaps, of trophic disturbances as well as the action of decomposing urine upon the skin. The second day after the crossed extension reflex was first noted in the deafferented leg in each case, a stiffness became perceptible in that leg. Within three or four more days, the stiffness developed to a marked degree, and remained undiminished. Twenty-two days after operation, both animals were given lethal amounts of ether; the rigidity still persisted. As Ranson

believes, this would certainly preclude the possibility that the contracture was maintained by nervous action. It was doubtlessly due to a change in the muscles themselves.

In two cases, the ankle joint of the deafferented leg developed a marked instability. The exact time of onset was not noted, but the condition was apparently progressive, and after a month from the time of operation, the joint permitted both reversed motion and abnormal extension. The striking similarity to clinical cases of Charcot's joints in tabes, where, interestingly, the posterior roots are primarily involved, is suggestive.

2. Preparations with one hind leg deafferented and the opposite one denervated

In the five cats in which one hind leg was deprived completely of somatic innervation, and the opposite one deafferented as usual, the denervated leg offered a control which may be assumed to represent a completely atonic condition. Such animals were best for study during the first few weeks after recovery from the operation, because, in time, muscular atrophy in the control limb would theoretically introduce an additional factor of difference between the two sides.

When these cats walked, using the fore legs and dragging the other two, the denervated leg was flaccid and motionless, whereas the deafferented leg gave feeble movements synchronous with corresponding ones of the diagonally opposite extremity. While the animal was suspended by the neck, the deafferented leg was often pulled markedly higher than the denervated one, due to stimuli from other portions of the body. When the animal was quiet, the deafferented leg sank to a flaccid level, unless another movement was interposed. If passively pulled down to the level of the opposite denervated leg, it remained there until the cat was disturbed and other afferent stimuli produced.

In the quiet animal both hind legs appeared to be equally and completely atonic. There was no deviation of the pelvis to either side, nor any adduction of either leg. None of the denervated extremities showed the phenomenon of contracture, which is especially interesting, since these legs remained always inactive. It seems certain, therefore, that the efferent innervation plays an essential rôle in the production of contracture.

3. Preparations with both hind legs deafferented

In cats with both hind legs deafferented, the crossed extension reflex was uniformly absent, and with the animal at rest, both extremities were conspicuously atonic. In two individuals, however, marked progression movements appeared a few hours after the operation and became maximum within twenty-four hours; at this time both hind legs were dragged along, making large excursions of alternate flexion and extension. It was obvious, as might be expected, that each movement was sychronous with a corresponding one of the diagonally opposite leg. With the animal suspended by the neck, reflex extension could be elicited in either hind leg, by passive extension of the contralateral fore leg, or flexion of the homolateral one. Unfortunately, two days later when the study was to be resumed, such responses were practically absent. Just why these phenomena largely disappeared in the chronic preparation is not clear.

Bilateral preparations of this kind are especially suitable for studying tonic neck and labyrinthine reflexes without decerebrating the animal, because with each leg responding in turn, as the head is rotated through 180 degrees, the contrast between the two is doubly prominent.

4. Decerebrate preparations

Three animals which had survived the original operation for 69, 76, and 77 days respectively were decerebrated. Each developed a profound rigidity within thirty minutes; they remained alive for several hours. The deafferented leg, however, was always flaccid. Numerous reflexes, many of which had been elicited only occasionally before decerebration now occurred, greatly augmented and with unfailing regularity. Influences from the neck and labyrinths, as well as from the opposite hind leg and each of the fore legs were especially prominent. Responses were exhibited by both the control and the deafferented legs, but in the latter were markedly increased in force and extent.

Magnus de Kleyn neck and labyrinthine reflexes. With the cats placed upon their backs, stimuli were produced by rotating the head or bending the neck ventrally, dorsally, or laterally. When the head

was rotated toward the injured side, or flexed ventrally, and held in this position, a strong extension of the deafferented leg occurred, followed after a brief latent period by sudden but incomplete relaxation. With the neck fixed in the new position, the leg exerted a continuous residual extensor force. Upon removing the stimuli arising from the static neck posture, by bringing the head back to the central axis of the animal, the deafferented leg became suddenly flaccid. Hence static neck reflexes appeared to produce in deafferented muscles one of the characteristics of tonus, namely, sustained contraction. With this in mind, the condition was examined more carefully. When the deafferented limb was compared with the normal one, extended with equal force, a difference was at once evident. In the normal leg, there was the usual decerebrate plasticity; in the deafferented one, an elastic resistance, with no tendency of the muscles to hold new lengths conferred upon them. Sherrington (1909) produced a very similar type of contraction in the deafferented vastocrureus muscle by electrical stimulation of nerves to the opposite leg.

Upon bending the head dorsally, the fore legs became sharply extended, while the hind legs dropped passively into flexion. The normal hind limb in this relaxed condition still felt plastic; the deafferented one, completely flaccid. The difference was unmistakable. Lateral rotation, or movement of the head in the sagittal plane, produced both neck and labyrinthine impulses simultaneously. Bending the neck laterally produced stimuli from the deep neck musculature alone, while dropping the animal though space with the neck fixed in relation to the body gave impulses exclusively of labyrinthine origin. The deafferented leg responded to each influence separately, and the present observations closely follow the principle of Magnus (1925), that when the two sets of influences act simultaneously, there is approximately an algebraic summation in the resulting responses.

Reflexes in the deafferented leg arising from the other legs. The crossed extension reflex was prominent in the deafferented leg before decerebration; but following decerebration, it became still more pronounced. Moreover, as repeatedly noted above, sudden contraction and abrupt relaxation occurred in rapid succession. It was possible to examine, separately, reflexes in the deafferented leg, arising from each of the fore legs, by holding one fore leg immobile, while the other was moved

passively. Extension of the contralateral fore leg was reflected in the operated extremity by strong extension. On the other hand, flexion of the contralateral fore leg, or extension of the fore leg on the same side,

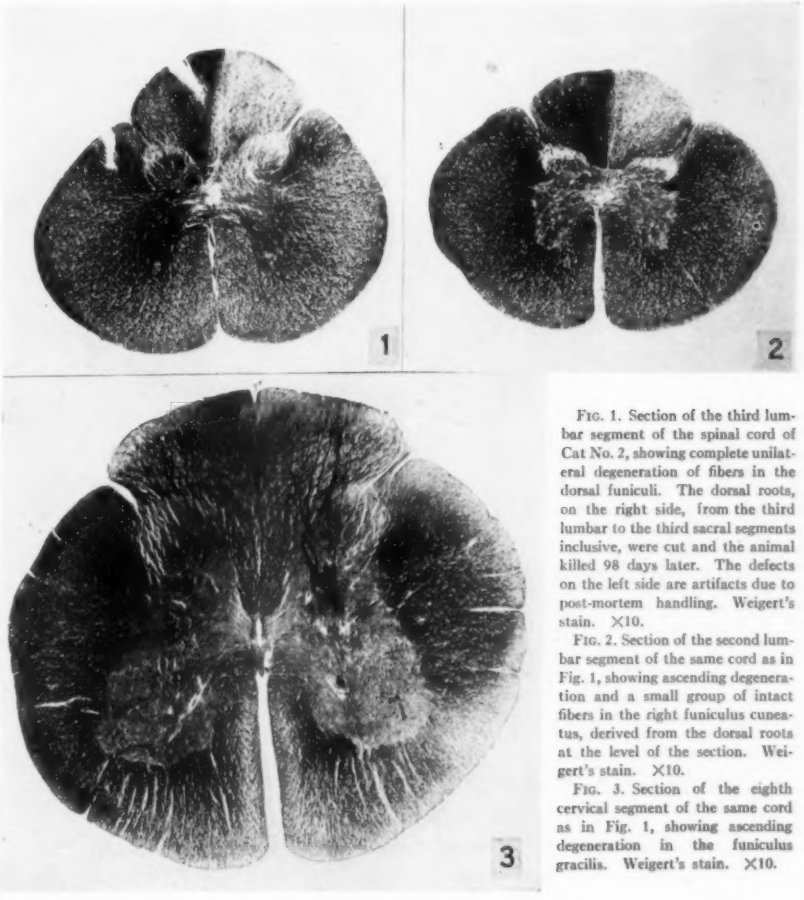


FIG. 1. Section of the third lumbar segment of the spinal cord of Cat No. 2, showing complete unilateral degeneration of fibers in the dorsal funiculi. The dorsal roots, on the right side, from the third lumbar to the third sacral segments inclusive, were cut and the animal killed 98 days later. The defects on the left side are artifacts due to post-mortem handling. Weigert's stain. ×10.

FIG. 2. Section of the second lumbar segment of the same cord as in Fig. 1, showing ascending degeneration and a small group of intact fibers in the right funiculus cuneatus, derived from the dorsal roots at the level of the section. Weigert's stain. ×10.

FIG. 3. Section of the eighth cervical segment of the same cord as in Fig. 1, showing ascending degeneration in the funiculus gracilis. Weigert's stain. ×10.

gave less certain results. When stepping movements were imposed upon the fore legs, by combining flexion of the one with extension of the other, two sets of stimuli occurred simultaneously and there was a

pronounced summation in the responses; the deafferented leg underwent prominent excursions, of alternate flexion and extension, each phase being identical with that of the contralateral fore leg.

In one decerebrated animal, there developed in the control hind leg a clonic spasm, from some undetermined cause. At the same time, the deafferented limb was held in forceful and sustained extension. However, when the opposite leg was grasped firmly enough to prevent all clonic motion, the deafferented one collapsed at once into complete flaccidity. This was observed repeatedly, and is an excellent example of a type of sustained reflex contraction in deafferented muscles that may readily simulate tonus.

In summary, it may be said that in the decerebrate preparation, the deafferented leg developes no decerebrate rigidity, whereas it exhibits reflexes differing from those of the opposite leg in two outstanding regards: they are increased in force and amplitude, and are wholly unsustained after the stimulus is withdrawn.

5. A study of sections of the spinal cord

Sections of the spinal cords were prepared for microscopic examination. In six individuals, Weigert-stained sections showed degenerations clearly. In the others, sufficient time had not elapsed, since the operation, to obtain the best results from the Weigert method. In every case, hematoxylin and eosin preparations showed degeneration, as well as in some instances, tissue defects, enlargements of the central canal, and areas of infiltration with mononuclear cells.

Sections at the third lumbar level, which was just at the upper boundary of the operated portion, always showed complete degeneration of fibers on the dorsal funiculi on the deafferented side. This degeneration could be clearly traced into the thoracic and cervical regions as shown in figures 1, 2 and 3. This demonstrated clearly that no dorsal roots had escaped being cut.

A study of these sections supports the conclusion that it is not possible to cut dorsal roots intradurally without demonstrable damage to the cord. In each case, some scattered degenerated fibers were seen, in addition to those in the posterior funiculi on the operated side. However, differences in relative amounts of injury are very striking

and lend themselves to positive correlation with some of the variations seen in the living animals, such as contracture and bladder incontinence.

In the three cords purposely injured at the time of operation, the preponderance of damage over that in any of the others is unmistakable. In two instances, sections at the sixth lumbar segment show a cut extending into the posterior horn, partially filled with cellular

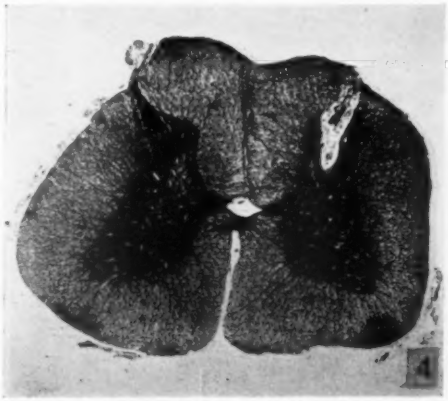


FIG. 4. SECTION OF THE SIXTH LUMBAR SEGMENT OF THE SPINAL CORD OF CAT NO. 18, TWENTY-TWO DAYS AFTER THE OPERATION, SHOWING EXTENSIVE INJURY EXTENDING INTO THE DORSAL HORN

The dorsal roots were cut on the right side from the third lumbar to the third sacral segments inclusive, and the cord deliberately injured. The animal developed severe bladder incontinence, and rigidity of the deafferented limb. Haematoxylin and eosin. ×10.

debris. At the same time, there is considerable dense infiltration of mononuclear cells about the lesion, and extending well into the gray matter (figs. 5 and 6). In the third individual, the injury was less severe, but here, too, diffuse infiltration indicates clearly a myelitis.

In only one of the animals in which the cord was not purposely injured is there evidence of more than slight undue degeneration. In this one case, the upper margin of the dural incision had apparently compressed the dorsal portion of the cord. Weigert-stained sections

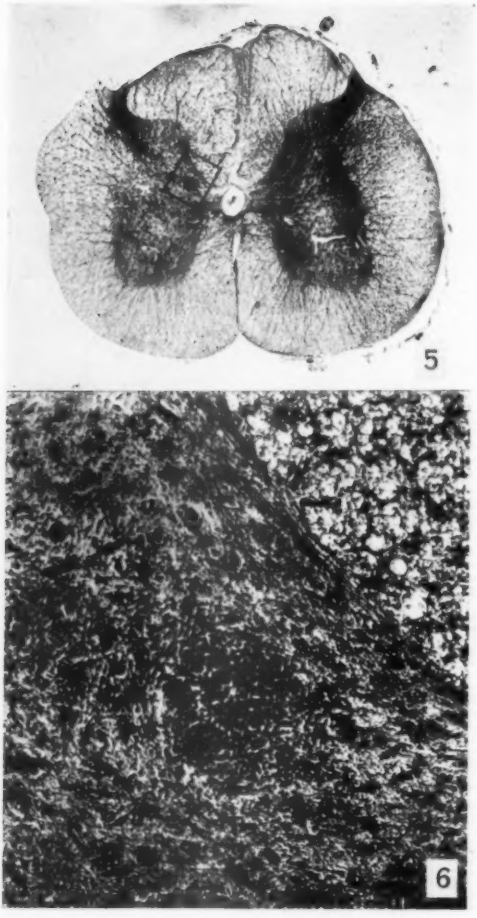


FIG. 5. SECTION OF THE SIXTH LUMBAR SEGMENT OF THE SPINAL CORD OF CAT NO. 19, TWENTY-TWO DAYS AFTER THE OPERATION, SHOWING AREAS OF DENSE INFILTRATION INDICATING A MYELITIS

The dorsal roots were cut on the left side, from the third lumbar to the third sacral segments inclusive, and the cord purposely injured. The animal developed severe bladder incontinence, and rigidity of the deafferented limb. Haematoxylin and eosin. ×10.

FIG. 6. HIGHER MAGNIFICATION OF THE AREA OF DENSE INFILTRATION SHOWN IN FIGURE 5 (INDICATED BY THE SMALL RECTANGLE)

Haematoxylin and eosin. ×125

in the third lumbar segment show a gross distortion of the posterior columns and extensive degeneration in the dorsal funiculi of the unoperated as well as of the operated side. There is no damage visible in any other portion of the cord. In this particular cat, there was no evidence of any visceral disturbance, and the limb of the opposite side showed no impairment whatever.

DISCUSSION

The absence of tonus in deafferented muscles

Observations upon the deafferented limb at rest, and upon the character of its movements are both useful in determining the functional alterations which the leg musculature has undergone. With the entire animal at rest, the deafferented muscles show a reduction of tonus perceptibly greater than that ever reached by the normal muscles, and equal to that which they undergo upon being severed from all nervous connections. This is clearly brought out in cats with one hind leg deafferented, the other denervated. A similar loss of tonus appears in the musculature of the pelvic girdle. When one side is deafferented, atonus of the muscles on that side permits the normal tonic antagonists of the opposite side to pull the pelvis into an abnormal posture.

The movements of such a leg are abrupt and exaggerated, and the usual smoothness of transition between extremes of tension is conspicuously absent. This does not mean that its contractions may not in some cases be sustained. Reflex stimuli in states of excitement with rapid movements of the normal extremities may come in rapid succession, giving tetanic responses, but the release, when stimulation ceases, is so abrupt that it presents a striking contrast to the activity of normal tonic muscle.

Predominance of extensor reflexes

Decerebrate rigidity is predominantly a phenomenon of the extensor muscles. Ranson observed an overaction of the extensors in the deafferented leg and regarded it as evidence of a similar hypertonus. He believes that this is sufficiently great to prevent proper use of the flexors. In the present experiments this has been carefully considered, and a different interpretation seems more likely, namely, that the

tendency of the deafferented leg to exhibit more extensor than flexor movements depends upon the preponderance of adequate stimuli for extension. The evidence for this will now be considered in detail.

In the first place, it was shown that marked flexion, unhampered by any spasticity, occurs frequently, when there are adequate stimuli from other portions of the body. In attempting to reach the hand holding its neck, the animal flexes the deafferented leg to that height. Progressive movements in the normal legs are reflected in marked flexor as well as extensor beats of the deafferented extremity.

Flexor responses are considered to be phylogenetically old, and are essentially responses of a leg to noxious stimuli from the periphery. When the exteroceptive impulses from the leg itself are cut off, the adequate stimuli for flexor responses are markedly decreased. This is clear when the foot-pad of the normal hind leg is touched. A quick flexion of the leg occurs in every case. This is accompanied in the opposite hind leg by a crossed extension.

The predominance of extensor responses observed in the deafferented leg is derived, in a large measure, from this crossed extension reflex. The crossed extension reflex, forming an adequate basis for postural balance in opposing extremities, is much easier to elicit than a crossed flexor reflex. Sherrington (1909) found that whereas the lengthening reaction in a muscle is always accompanied by strong extension of the crossed knee, any such crossed flexion accompanying the shortening reaction is difficult to obtain. The crossed extensor reflex is more easily demonstrated in the deafferented than in the normal limb. This suggests that the action of the intrinsic afferent impulses may normally oppose and moderate the extent of reflexes.

After close observation, it is clear that the crossed extension reflex is brought out in these preparations in essentially the same pattern with procedures that appear at first to be somewhat different. Thus, pinching the foot-pad of the opposite hind leg produces an extension. Moreover, placing the foot-pad of the normal hind leg in contact with the table causes the deafferented leg to extend strongly, and finally, if the cat is placed upon its feet, impulses from the normal hind leg cause the opposite one to be abnormally extended. Because of its exaggerated character, and the many frequently recurring ways in which this crossed extension is obtained, the deafferented leg may readily appear

to be abnormally extended. However, when both hind legs are deafferented, or when one is deafferented and the other denervated, the crossed extension reflex is obviated, and in these cats extensor reflexes in the deafferented extremity are no more prominent than those of the flexors, except in as much as, in most positions, the action of gravity upon the leg favors passive extension.

The types of stimuli that reach the deafferented leg to produce extension may now be enumerated. Extension is often produced by stimulation of the opposite hind leg, as has already been stated. It also occurs when the labyrinths are stimulated by allowing the animal to suddenly drop a few inches. Strong flexion of the head, or turning the head to the same side, also produces extension. Finally, extension of the deafferented leg is brought about by flexion of the foreleg of the same side or extension of the opposite fore leg. This coördination with the fore legs plays an important rôle in the alternate rhythm of normal progression.

Flexion, on the other hand, is produced in the deafferented leg by flexion of the opposite fore leg, or extension of the fore leg of the same side. These responses are particularly clearly seen after decerebration and again indicate the mutual interaction of all of the limbs in normal progression. Flexion is also produced, in the deafferented hind leg, by extreme extension of the head, or by turning or rotating the head sharply to the opposite side.

Whereas the crossed extension reflex is extremely prominent, and is brought out in numerous ways in the course of the usual behavior of the animal, few if any flexor responses are ever elicited by stimulation of the opposite hind leg. Theoretically, extension of the normal hind leg should produce flexion of the deafferented one, but such a response is always difficult to obtain (Sherrington, 1909). Furthermore, the very important group of flexor movements, namely, those that normally occur in response to local exteroceptive stimuli, are of course entirely lost.

This preponderance of extensor reflexes remaining intact in the deafferented leg gives an overaction of the extensors fundamentally quite different from the reflex standing of a decerebrate preparation. In the case of decerebrate rigidity, each posture derived from a reflex or passive movement is notably sustained; in the deafferented leg, following

each reflex, the resultant posture of the leg is left wholly to the action of external forces, until another reflex is initiated.

Contracture

The permanent irreversible rigidity which developed in the leg muscles of a few animals in this series is still unexplained. Certain facts, however, regarding its etiology, seem clear. The integrity of the ventral roots is essential, and there is a much lower threshold for the development of this type of contracture in the deafferented than in the opposite normal leg, which is doubtless influenced by the same abnormal stimuli from the cord. In the present experiments this type of muscle rigidity is consistently associated with relatively great injury to the spinal cord, as shown by marked bladder disturbances and microscopic evidences of extensive damage. Cats in which the cord is injured experimentally, develop, without exception, contracture in the deafferented leg. The relation of this muscular rigidity to cord injury suggests that it is an irritative phenomenon. Mere immobility of the limb cannot be a primary condition for such rigidity, because the condition did not occur in any case of complete paralysis produced by severing both dorsal and ventral nerve roots. In all of the present experiments, the contracture failed to disappear after complete ether narcosis and death of the animal. It must be concluded, therefore, that it involves an irreversible change in the muscle itself. It is not unlikely that there is an incipient stage of muscle spasm which would relax upon severing nervous connections, but this has not been demonstrated. If a similar irritative contraction occurs in normal muscles, it doubtless at once stimulates afferent fibers to exert a protective inhibitory influence, counteracting those irritative impulses to which the muscles are subjected. In the absence of afferent fibers this irritation produces more permanent injury. There is no reason, however, to identify this process in any way with normal postural contraction. The position of such a muscle is rigidly held, but the plasticity and adjustability that characterize normal tonus are wholly absent.

The rôle of the dorsal roots in muscle tonus and animal posture

Sympathetic nerve fibers are apparently eliminated from consideration as a source of tonic impulses by considerable evidence. More-

over, the work of Coman (1926), appears, likewise, to rule out antidromic fibers in the dorsal roots as a factor in the control of tonus, and at the same time to demonstrate that the ventral roots constitute the efferent pathway for tonus. All motor impulses to striated musculature must be conveyed by somatic motor fibers. To divide the responses into plastic and contractile, or tonic and phasic, implies qualitative differences, whereas there is ample reason to believe that these differences are only quantitative. From the fact that varied afferent stimuli, including those involved in tonus, must employ one efferent final common pathway, it may be readily inferred that they can elicit only a final common response—presumably an all or none contraction of the muscle fibers.

By this same argument, and in the light of the present experiments, it is suggested that tonus derives its fundamental distinction, not from a special efferent pathway, but purely from the afferent side of the arc. Only through intrinsic afferent fibers, in intimate relation with the contracting muscles, can the proper stimuli be received for continuous adjustments of muscles to slightest changes of tension, for such stimuli occur only locally. In as much as a contraction of the deafferented muscles is far reaching enough to change the whole posture of the animal, and normal muscles throughout the body respond to the new postural demands, proprioceptive stimuli are, of course, derived from the latter. By this roundabout sequence of events, gross postural adaptations may be secondarily made by deafferented muscles. Likewise, a change in the position of the neck elicits a gross compensatory contraction in the muscles of the operated leg. But the responses to impulses from the labyrinths and deep neck musculature, strictly interpreted, merely confer postures on deafferented muscles, whereas tonus is essentially a maintenance of posture.

The tonus of each muscle is derived from intrinsic reflexes, as shown in the highly controlled experiments of Sherrington (1909); posture of the animal as a whole is, in turn, derived from a coördinated distribution of this local tonus, augmented in some muscles, diminished in others. The latter integration is accomplished through such superimposed influences as those from the labyrinths, and deep neck musculature.

SUMMARY

In twenty adult cats, the dorsal roots from the third lumbar to the third sacral nerves inclusive, were cut, intradurally, and proximal to the ganglia. The altered properties of the legs thus deafferented were studied from ten to ninety-eight days after the operation. Responses in the deafferented leg derived from stimuli produced in each of the other legs, in the neck, and in the labyrinths, were separately identified. These responses showed two striking characteristics: increased force and extent and abrupt relaxation following the cessation of extrinsic stimulation.

When cord injury was minimal, as shown by the absence of bladder incontinence, and by the subsequent examination of microscopic sections, atonus was manifested in the deafferented muscles in the following ways: (1) The deafferented leg at rest was as flaccid (unresistant to manipulation) as the opposite denervated leg. (2) Reflex contractions were sudden and exaggerated, but lacked conspicuously the gradual transition between extremes of tension, so characteristic of tonic muscles. (3) After decerebration, there was no decerebrate rigidity in the deafferented muscles, no lengthening or shortening reaction, no trace, on palpation, of the usual condition of plasticity. (4) The deafferented muscles of the lower spine and pelvic girdle permitted the tonic antagonists of the opposite side to pull the pelvis laterally into a distorted posture.

In two cats, irreversible rigidity or contracture developed in the deafferented leg; the same condition was experimentally produced in three more animals by injuring the spinal cord. The following facts regarding this phenomenon were demonstrated: it is the result of cord injury; the efferent innervation is essential; and in the absence of local afferent nerves, there is a lower threshold for its occurrence.

REFERENCE

BROWN, T. GRAHAM. 1912 The intrinsic factors in the act of progression in the mammal. *Proc. Roy. Soc.*, B, lxxiv, 308.

COMAN, F. D. 1926 Observations on the relations of the sympathetic nervous system to skeletal muscle tonus. *Johns Hopkins Hospital Bull.*, xxxviii, 163. *Idem* 1928 Observations on a supposed rôle of the dorsal roots in muscle tonus. *The Anatomical Record*, xxxviii, no. 1, 42.

FRANK, E. 1920 Die Parasympatische Innervation der quergestreiften Muskulatur und ihre klinische Bedeutung. *Berliner Klinische Wochenschrift.*, lvii, 725.

FULTON, J. F. 1926 Muscular contraction and the reflex control of movement. Baltimore, Williams and Wilkins Co.

LIDDELL, E. G. F., AND SHERRINGTON, C. S. 1924 Reflexes in response to stretch (myotatic reflexes). *Proc. Roy. Soc.*, B, xcvi, 242.

MAGNUS, RUDOLF 1924 Körperstellung. Verlag von Julius Springer, Berlin.

Idem 1925 Croonian Lecture—animal posture. *Proc. Roy. Soc.*, Series B, xcvii, 339.

RANSON, S. W. 1928(a) The rôle of the dorsal roots in muscle tonus. *Arch. Neur. and Psychiatry*, xix, no. 2, 201.

Idem 1928(b) Local tetanus. *Arch. Neur. and Psychiatry*, xx, no. 4, 663.

SHERRINGTON, C. S. 1906 The integrative action of the nervous system. Yale Univ. Press.

Idem 1909 On plastic tonus and proprioceptive reflexes. *Quar. Jour. Exp. Physiol.*, ii, 109.

Idem 1915 Postural activity of muscle and nerve. *Brain*, xxxviii, 191.

BOOK REVIEWS

Bacterial Vaccines and Their Position in Therapeutics. By LEONARD S. DUGDEON, C.M.G., C.B.E., F.R.C.P., London. 87 pp. $2.50. (*Paul N. Hoeber Inc., New York, 1928.*)

The author has given us a well written brief monograph of nine chapters. He begins his subject by discussing the principles of active immunization with bacterial vaccines. He describes the preparation of such vaccines and makes suggestions as to dosage. It is refreshing to read this monograph, chiefly because the author is conservative in his appraisal of the efficacy of any one particular type of vaccine in the treatment of disease. His conclusions are reliable and the reader can gather from this book a worthwhile summary of the subject of bacterial vaccines.

L. N. G.

Review of Statistical Methods for Research Workers. By R. A. FISHER. Second Edition, pp. 41–269. 1928. (*Oliver and Boyd, London.*)

An elementary knowledge of statistical methods is an asset to the laboratory worker in all of the basic medical sciences. Experimental efforts result in the accumulation of data which must be interpreted. Before experimental deviations between sets of data can be claimed to be significant, proof must be produced that such deviations are greater than can be expected by simple sampling. Description of sampling deviations is most easily obtained by application of statistical methods. R. E. Fisher attempts to present his subject in a simple manner so that the non-mathematical reader can grasp his meaning. He does this without violation of the postulates on which the significance of statistical methods are based. This does not mean that the book will be clear to the casual reader. Of necessity the author uses a considerable number of symbolic mathematical terms. However, such terms and words are usually accompanied by definitions which, if they are comprehended, make the book less formidable to the non-mathematical reader

Chapter 2 offers an adequate explanation of the most essential features in the graphic methods, namely; rates, correlation, frequency diagrams, and the use of arith-logarithmic paper.

Chapter 3 describes the normal frequency distribution and demonstrates how the best fitted normal curve can be obtained. The binomial disturbance which approaches the normal curve as its limit is discussed and illustrated.

Chapter 4 offers what is probably the best explanation of Chi-square which can be found in any statistical textbook. Illustrations of how to compute Chi-square and how to use it are included.

The non-mathematically trained research worker will find that the last part of the book is more difficult to understand. This is due in part to the use of a consid-

erable number of mathematical symbols and in part to the increased complexity of the subject matter considered.

From an applied as well as a diagnostic standpoint the value of the book can hardly be overestimated.

H. L. D.

Diseases of the Thyroid Gland. By ARTHUR E. HERTZLER, M.D. 286 pp. $7.50. (*C. V. Mosby Co., St. Louis, 1929.*)

This second edition of Dr. Hertzler's book is dedicated to Henry S. Plummer, M.D., "in expression of appreciation for the great service he has rendered goiter surgeons." It is written in an informal, almost narrative style.

Although the author states in the preface that it is toward the chapters dealing with the pathology of the thyroid gland that he desires to draw special attention, one feels that the sections on symptomatology and clinical diagnosis are the strongest parts of the book. The author's pathological classification of the thyroid diseases is not in accordance with the generally accepted views. On the other hand, the chapters dealing with the diagnosis and care of the patient contain many helpful and practical hints. The volume includes a section on operative technique by Victor E. Chesky, M.D.

The author makes the following rather summary statements: "The fact is established beyond controversy that Basedow's is, first to last, a disease of the thyroid gland. Basedow's disease without changes in the thyroid gland does not exist." (Page 25.) "As far as any knowledge now available is able to guide us, it is safe to say that the surgical cure of goitre is permanent and safe." (Page 179.) "Protein in the diet of a case of Graves' disease should be minimal." (Page 211.) "To carry animal experimentation to the explanation of human disease is at best a precarious premise and, I believe, is not warranted." (Page 61.)

B. W.

Laboratory Diagnosis and Experimental Methods in Tuberculosis. By HENRY STUART WILLIS. With a Chapter on Tuberculo-Complement Fixation. By J. Stanley Wooley. Introduction by Allen K. Krause. 330 pp. $3.50. (*Charles C. Thomas, Springfield, 1928.*)

This book can be recommended without qualification to anyone who seeks information regarding the best methods of working first-hand with the tubercle bacillus, whether in the diagnostic or in the experimental laboratory. It contains an excellent selection of reliable methods of demonstrating the presence of tubercle bacilli, wherever they may be, in any material available for diagnostic examination; there is a critical presentation of the best methods of performing diagnostic tests which depend upon the altered reactivity of the infected body; and there is an excellent and detailed description of the procedures which should be mastered by anyone who wishes to investigate experimentally the unsolved problems of tuberculosis. The methods included in this book are those which the author has found to be the most reliable during his long experience with matters pertaining to the tubercle bacillus.

In his analysis of the value of the various diagnostic tests, Dr. Willis has displayed a judicious reserve which is pleasant to meet with in a book devoted to laboratory methods. His attitude throughout is thoroughly sound, and is refreshing in contrast with the extravagant and exaggerated claims so often made for many of the tests by uncritical enthusiasts, and by the great army of those who cling to the hopeless hope that the easy road of laboratory diagnosis can be substituted for the arduous pathway leading to clinical perfection. His point of view is in keeping with that recently expressed by Dr. Thayer in the concluding sentences of his Bright Lecture,—sentences which, in this age infested with laboratory clinicians, the young aspirant toward true clinical distinction cannot too early appreciate as containing a precious guiding principle:

"The art of diagnosis may not be acquired by the contemplation of radiograms, by the perusal of reports of studies of tissues, body fluids, secreta and excreta, or by the critical consideration of data accumulated by others. . . . . Scientific methods have contributed much to medicine. But after all how far we are from the day when medicine may be practiced by rule of thumb! . . . . All this new and precious technique supplements, it does not supplant, the fundamental procedures of observation and physical examination of which Laennec and Bright made use. And we must not forget that a thorough training in the fundamental art of physical exploration is as vital as ever, that the necessary period of experience spent at the bedside of the patient has not been shortened by a day."

A. R. R.

Diseases of the Ear, Nose and Throat, Medical and Surgical. By WENDELL CHRISTOPHER PHILLIPS, M.D. Seventh revised and enlarged edition. Illustrated. 922 pages. $9.00. (*F. A. Davis Company, Philadelphia, 1928.*)

As he states in his preface, Dr. Phillips has deviated from the usual order of arrangement by giving the Ear the first place in this seventh edition. In so doing he succeeds in placing the desired emphasis on Otology and has achieved a very admirable and practical discussion of this subject. The parts dealing with Rhinology and Laryngology are somewhat less praiseworthy.

One of the most interesting features of the book is a consistent attempt to present the modern conception of "foci of infection" as bearing on general systemic diseases. This tends to broaden the field for the specialist but at the same time adds to his responsibilities in diagnosis and therapy.

For the medical student and practitioner this is a very useful book. The details of equipment, methods of examination, and instrumentation, are well handled. The author inculcates a proper respect for surgical technique and the descriptions of operative procedures are clear. Usually a choice of approved methods is presented. For the various diseases a very satisfactory clinical picture is given, but in many instances the pathology and therapy are rather sketchy.

The illustrations are quite helpful and fairly accurate. A good index makes the subject matter readily accessible.

H. R. S., JR.

BOOKS RECEIVED

Clinical Laboratory Methods. By RUSSELL LANDRAM HADEN, M.A., M.D. With 69 illustrations and 4 color plates. Third edition. 1929. 8°. 317 pages. C. V. Mosby Company, St. Louis. $5.00.

Principles and Practice of Electrocardiography. By CARL J. WIGGERS, M.D. With 61 illustrations. 1929. 8°. 226 pages. C. V. Mosby Company, St. Louis. $7.50.

Osteomyelitis and Compound Fractures and Other Infected Wounds. Treatment by the Method of Drainage and Rest. By H. WINNETT ORR, M.D., F.A.C.S. Illustrated. 1928. 8°. 208 pages. C. V. Mosby Company, St. Louis. $5.00.

Otosclerosis. A Résumé of the Literature to July 1928. Compiled under the direction of the Committee on Otosclerosis, American Otological Society. Norval H. Pierce, M.D., Eugene A. Crockett, M.D., James F. McKernon, M.D., J. Gordon Wilson, M.D., Arthur B. Duel, M.D., Editor. Volumes I and II. 1929. 8°. 706 pages. Paul B. Hoeber, Inc., New York. $15.00.

Collected Papers of the Mayo Clinic and the Mayo Foundation. Edited by Mrs. M. H. Mellish, Richard M. Hewitt, B.A., M.A., M.D., and Mildred A. Felker, B. S. Volume XX, 1928. Published June, 1929. 8°. 1197 pages. W. B. Saunders Company, Philadelphia. $13.00.

Gynecology. A Textbook of the Diseases of Women. By LYNN LYLE FULKERSON, A.B., M.D., F.A.C.S. With six hundred twelve illustrations, three in color. 1929. 8°. 842 pages. P. Blakiston's Son and Company, Philadelphia. $9.00.

The History of Hemostasis. By SAMUEL CLARK HARVEY, M.D. With 19 illustrations. 1929. 12°. 129 pages. Paul B. Hoeber, Inc., New York. $1.50.

An Introduction to the Study of Physic. [Now for the first time published]. By WILLIAM HEBERDEN [1710–1801]. A Prefatory Essay by Leroy Crummer. With a Reprint of Herberden's 'Some Account of a Disorder of the Breast.' Portrait in Photogravure. Six illustrations. 1929. 12°. 159 pages. Paul B. Hoeber, Inc., New York. $2.00.

The Clinical Aspects of Venous Pressure. By J. A. E. EYSTER, B.Sc., M.D. 1929. 8°. 135 pages. The MacMillan Company, New York. $2.50.

Modern Methods of Feeding in Infancy and Childhood. By DONALD PATERSON, B.A., M.D. (Edin.) M.R.C.P. (Lond.), and J. FOREST SMITH, M.R.C.P. (Lond.). Second Edition. 1929. 8°. 149 pages. Modern Medical Monographs. Edited by Hugh MacLean, M.D., D.Sc., F.R.C.P. Paul B. Hoeber, Inc., New York. $3.00.

Nursing Mental Diseases. By HARRIET BAILEY, R.N. Second edition, completely revised. 1929. 12°. 294 pages. The MacMillan Company, New York. $2.00.

The Treatment of Fractures. By LORENZ BÖHLER, M.D. Authorized English Translation by M. E. Steinberg, M.S., M.D., of Portland, Oregon. With 234 illustrations. 1929. 8°. 185 pages. Wilhelm Maudrich, Vienna.

Reports from the Laboratory of the Royal College of Physicians, Edinburgh. Edited by Sir Robert Philip, M.D., LL.D., Hon. F.R.C.S. and Anderson Gray McKendrick, M.B., D.Sc. Volume XVII. 1929. 8°. 110 pages. Oliver & Boyd, Edinburgh.

Arthritis and Rheumatoid Conditions. Their Nature and Treatment. By RALPH PEMBERTON, M.S., M.D. Illustrated with 42 engravings and 1 colored plate. 1929. 8°. 359 pages. Lea & Febiger, Philadelphia.

The Pressure Pulses in the Cardiovascular System. By CARL J. WIGGERS, M.D. With diagrams and illustrations. 1928. 8°. 200 pages. Monographs on Physiology. Longmans, Green & Company, New York. $5.00.

A Manual of Diseases of the Nose, Throat, and Ear. By E. B. GLEASON, M.D., LL.D. Sixth edition thoroughly revised. 1929. 12°. 617 pages. W. B. Saunders Company, Philadelphia. $4.50.

Volksgesundheit im Krieg. Herausgegeben von Prof. Dr. Clemens Pirquet. Wirtschafts- und Sozialgeschichte des Weltkrieges. Professor Dr. James T. Shotwell. I. and II. Teil. 1926. 8°. (I. Teil, 428 Seiten) (II. Teil, 330 Seiten). Hölder-Pichler-Tempsky A. G., Wien.

October Views in Medicine. Read at a dinner of the Innominate Society, Louisville, Ky., Dec. 28, 1928. By WM. ALLEN PUSEY, M.D., LL.D. 1929. 16°. 19 pages. American Medical Association Press, Chicago.

A History of the Medical Department of the United States Army. By P. M. ASHBURN, Col., Medical Corps, U. S. Army. With an introduction by Surgeon General Merritte W. Ireland. 1929. 8°. 448 pages. Houghton Mifflin Company, Boston. $5.00.

Bacteriology for Nurses. By MARY A. SMEETON, B.Sc. (Columbia Univ.) R.N. Third edition revised. 1929. 8°. 335 pages. The MacMillan Company, New York.

Squint. Its Causes, Pathology, and Treatment. By CLAUD WORTH, F.R.C.S. Sixth edition. 1929. 8°. 246 pages. P. Blakiston's Son & Company, Philadelphia. $3.50.

International Clinics. A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. Edited by Henry W. Cattell, A.M., M.D., with the collaboration of Chas. H. Mayo, M.S. Thirty-ninth series, volume II. 1929. 8°. 305 pages. J. B. Lippincott Company, Philadelphia.

Physical Therapeutic Technic. By FRANK BUTLER GRANGER, A.B., M.D. With a Foreword by William D. McFee, M.D. Illustrated. 1929. 8°. 417 pages. W. B. Saunders Company, Philadelphia. $6.50.

The Neuroses. By ISRAEL S. WECHSLER, M.D. 1929. 8°. 330 pages. W. B. Saunders Company, Philadelphia. $4.00.

Recent Advances in Ophthalmology. By W. STEWART DUKE-ELDER, M.A., B.Sc. (St. And.), Ph.D. (Lond.), M.D., Ch.B. F.R.C.S. Second Edition. With 4 coloured plates and 110 text figures. 1929. 12°. 405 pages. P. Blakiston's Son and Company, Philadelphia. $3.50.

Les Courants Continus et les Courants Faradiques. Par MM. L. Delherm et A. Laquerrière. Les Actualités Physiothérapiques. Tome 1. Électrothérapie. Part. 1. 1929. 12°. 90 pages. Gauther-Villars et Cie, Paris.

Lumière et Rayons Infrarouges. Par E. et H. Biancani. Les Actualités Physiothérapiques. Tome 4. Actinothérapie Part. 3. 1929. 8°. 177 pages. Gauther-Villars et Cie., Paris.

The Nose, Throat, and Ear and their Diseases. In original contributions by American and European authors. Edited by Chevalier Jackson, M.D., Sc.D., LL.D., F.A.C.S. and George Morrison Coates, A.B., M.D., F.A.C.S. Assisted by Chevalier L. Jackson, A.B., M.D. With 657 illustrations and 27 inserts in colors. 1929. 8°. 1177 pages. W. B. Saunders Company, Philadelphia. $13.00.

The Conquest of Cancer by Radium and Other Methods. By Daniel Thomas Quigley, M.D., F.A.C.S. Illustrated with 334 engravings. 1929. 8°. 539 pages. F. A. Davis Company, Philadelphia. $6.00.

Physician and Patient. Personal Care. Edited by L. Eugene Emerson. 1929. 8°. 244 pages. Harvard University Press, Cambridge.

The Challenge of Chronic Diseases. By Ernst P. Boas, M.D., and Nicholas Michelson, M.D. 1929. 12°. 197 pages. $2.50. The MacMillan Company, New York.

State Board Questions and Answers. By R. Max Goepp, M.D. Sixth edition, thoroughly revised. 1929. 8°. 754 pages. $6.00. W. B. Saunders Company, Philadelphia.

Physical Examination and Diagnostic Anatomy. By Charles B. Slade, M.D. Fourth edition, thoroughly revised. 1929. 12°. 196 pages. $2.00. W. B. Saunders Company, Philadelphia.

American Illustrated Medical Dictionary. With the Pronunciation, Derivation, and Definition. By W. A. Newman Dorland, A.M., M.D., F.A.C.S. Fifteenth edition, revised and enlarged. 1929. 8°. 1427 pages. $7.50. W. B. Saunders Company, Philadelphia.

Gynecologic Technic. By Thomas H. Cherry, M.D., F.A.C.S. With 558 half-tone and line engravings, from photographs and pen-and-ink drawings by the author. 1929. 8°. 678 pages. $8.00. F. A. Davis Company, Philadelphia.

Varicose Veins. With Special Reference to the Injection Treatment. By H. O. McPheeters, M.D., F.A.C.S. Illustrated with a half-tone and line engravings. 1929. 8°. 208 pages. $3.50. F. A. Davis Company, Philadelphia.

The Anatomy and Physiology of Capillaries. By August Krogh, Ph.D., LL.D. Revised and enlarged edition. 1929. 8°. 423 pages. $4.00. Yale University Press, New Haven.

The History of Nursing. By James J. Walsh, M.D., Ph.D. 1929. 12°. 293 pages. $2.00. P. J. Kennedy & Sons, New York.

Oxford Medical Publications. Publisher: Humphrey Milford, London. The following sixteen volumes.

The Principles of Electrotherapy and their Practical Application. By W. J. TURELL, M.A., D.M., B.Ch. (Oxon.), D.M.R. & E. (Cantab.). Second edition. 1929. 8°. 413 pages.

Artificial Sunlight and Its Therapeutic Uses. By FRANCIS HOWARD HUMPHRIES, M.D. (Brux.), F.R.C.P. (Edin.), M.R.C.S. (Eng.), L.R.C.P. (Lond.). L.M. (Rot., Dublin), D.M.R. & E. (Cantab.). Fifth edition. 1929. 8° 340 pages.

Gastro-Intestinal Diseases. Lectures delivered at the James Mackenzie Institute for Clinical Research, St. Andrews, Winter Session, 1927. Edited by PROFESSOR DAVID WATERSTON, M.A., M.D., F.R.C.S. (Edin.). 1928. 8°. 278 pages.

The Treatment of Fractures and Dislocations in General Practice. By C. MAX PAGES, D.S.O., M.S. (Lond.), F.R.C.S. and W. Rowley Birstow, M.B., B.S. (Lond.), F.R.C.S. Third edition. 1929. 8°. 284 pages.

Ker's Infectious Diseases. A Practical Textbook. Revised by CLAUDE RUNDLE, O.B.E., M.D. (Lond.), M.R.C.S. (Eng.), L.R.C.P. (Lond.), D.P.H. Third Edition. 1929. 8°. 614 pages.

Endocrine Disorders. By PROFESSOR HANS CURSCHMANN. With an introduction by Franz Prange, Doctor of Medicine and Philosophy, Assist. at the Med. Cl., Uiv. of Rostock i.m. 1929. 8°. 188 pages.

Some Principles of Minor Surgery. By ZACHARY COPE, M.S., M.D. (Lond.), F.R.C.S. (Eng.). 1929. 8°. 159 pages.

Diseases of the Larynx. Including Those of the Trachea, Large Bronchi, and Oesophagus. By HAROLD BARWELL, M.D. (London), F.R.C.S. (Eng.) Third edition. 1928. 8°. 278 pages.

Diagnosis and Treatment of Deformities in Infancy and Early Childhood. By M. F. FORRESTER-BROWN, M.S., M.D. (Lond.). With a foreword by Sir Robert Jones, Bart., K.B.E., C.B., F.R.C.S. 1929. 8°. 199 pages.

The Cytoarchitectonics of the Human Cerebral Cortex. By CONSTANTIN VON ECONOMO. Translated by Dr. S. PARKER. 1929. 8°. 186 pages.

Tweedy's Practical Obstetrics. Edited and largely re-written by BETHEL SOLOMONS, M.D., F.R.C.P.I., M.R.I.A. Sixth edition. 1929. 8°. 759 pages.

Oesophageal Obstruction. Its Pathology, Diagnosis and Treatment. By A. LAWRENCE ABEL, M.S. (Lond.), F.R.C.S. (Eng.). 1929. 8°. 234 pages.

Nephritis Its Problems and Treatment. By T. IZOD BENNETT, M.D. (London), F.R.C.P. 1929. 8°. 94 pages.

Tuberculosis. Its Prevention and Home Treatment. A Guide for the Use of Patients. By HYSLOP THOMSON, M.D., D.P.H. Third Edition. 1928. 12°. 99 pages.

Haemorrhoids. Their Aetiology, Prophylaxis and Treatment by Means of Injections. By ARTHUR S. MORLEY, F.R.C.S. Eng. Fourth impression revised and enlarged. 1929. 8°. 122 pages.

The Robert Jones Birthday Volume. A Collection of Surgical Essays. 1928. 8°. 434 pages.

INDEX TO VOLUME XLV

Amoss, Harold L. and Eleanor A. Bliss, The effect upon haemolytic streptococci of cultivating them in immune and normal serum 361
Amylase concentration in normal urine 105

Bliss, Eleanor A. and Harold L. Amoss, The effect upon haemolytic streptococci of cultivating them in immune and normal serum 361
Blood cells, Studies on the living, of the newborn 75
Book reviews 117, 189, 264, 331
Bundle branch block, A case of, confirmed by pathological study 40

Diphtheria, The circulatory failure of 276

Electrical resistance, Nervous control of the, of the skin 56

Ferree, C. E., G. Rand and M. M. Monroe, Errors of refraction, age and sex in relation to the size of the form field and preliminary data for a diagnostic scale 295
Finkelstein, Harold, and Walter Brem Mayer, Amylase concentration in normal urine 105
Flinn, F. B. and S. M. Seidlin, Parathormone in the treatment of "Radium Poisoning." A preliminary report 269
Forkner, Claude E., Studies on the living blood cells of the newborn 75
Friedenwald, Jonas S., Report of a case of herpes zoster ophthalmicus treated with convalescent serum 103
Friedenwald, Harry, and Jonas S. Friedenwald, The retinal blood vessels in hypertension and arteriosclerosis 232

Ginsberg, Leon, Sarcoid of Boeck in negro 108
Goitre, Studies in the reactions of simple, to iodine 215
Guttmacher, Manfred S., John Hunter, his enemies and his friends 15

Herpes zoster ophthalmicus, Report of a case of, treated with convalescent serum ... 103
Hunter, John, his enemies and his friends 15
Hypophyseal tumor, A case of, with associated tumor-like enlargement of the parathyroids and islands of Langerhans 1

Ileum, The bacterial flora and hydrogen-ion concentration of the lower human, the effect of lactose and acidophilus milk administration; and the possible relationship of ileal flora to chronic ulcerative colitis 315

Lloyd, Putnam C., A case of hypophyseal tumor with associated tumor-like enlargement of the parathyroids and islands of Langerhans 1

Longcope, W. T., The pathogenesis of glomerular nephritis..... 335

Machida, Kenji, Observations on the degeneration and regeneration of post-ganglionic nerve fibers..... 247
Malta fever in the United States..... 133
Marshall, E. K., The aglomerular kidney of the toadfish (Opsanus tau)..... 95
Mayer, Walter Brem, and Harold Finkelstein, Amylase concentration in normal urine..... 105
McGraw, Theodore A., Operations on the thyroid gland..... 172
Medical education, Some tenets of..... 203
Medical Society, Programs of the, of Johns Hopkins Hospital..... 116
Monroe, M. M., C. E. Ferree and G. Rand, Errors of refraction, age and sex in relation to the size of the form field and preliminary data for a diagnostic scale. 295

Nephritis, Chronic, following eclampsia..... 176
Nephritis, glomerular, The pathogensis of..... 335
Noel, William W. and Francis F. Schwentker, The circulatory failure of diphtheria. 276

Paulson, Moses, The bacterial flora and hydrogen-ion concentration of the lower human ileum; the effect of lactose and acidophilus milk administration; and the possible relationship of ileal flora to chronic ulcerative colitis..... 315
Peckham, C. H., Chronic nephritis following eclampsia..... 176
Post-ganglionic nerve fibers, Observations on the degeneration and regeneration of.. 247

"Radium Poisoning," Parathormone in the treatment of..... 269
Rand, G., C. E. Ferree and M. M. Monroe, Errors of refraction, age and sex in relation to the size of the form field and preliminary data for a diagnostic scale. 295
Reflexes, A study of, in the deafferented leg of the cat and their relation to tonus... 371
Refraction, Errors of, age and sex in relation to the size of the form field and preliminary data for a diagnostic scale..... 295
Retinal blood vessels, The, in hypertension and arteriosclerosis..... 232
Richter, Curt P., Nervous control of the electrical resistance of the skin..... 56

Sarcoid of Boeck in the negro..... 108
Schwentker, Francis F. and William W. Noel, The circulatory failure of diphtheria. 276
Seidlin, S. M. and F. B. Flinn, Parathormone in the treatment of "Radium poisoning." A preliminary report..... 269
Sprong, Wilbur L., A study of reflexes in the deafferented leg of the cat and their relation to tonus..... 371
Streptococci, haemolytic, The effect upon, of cultivating them in immune and normal serum..... 361

Taussig, Helen B., A case of bundle branch block confirmed by pathological study.. 40
Thyroid gland, Operations on the..... 172

Wainwright, Chas. W., Malta fever in the United States..... 133
Webster, Bruce, Studies in the reactions of simple goitre to iodine..... 215
Weed, Lewis H., Some tenets of medical education..... 203

BULLETIN
OF
THE JOHNS HOPKINS HOSPITAL

EDITORIAL BOARD

Edward P. Carter
Alan M. Chesney
Arnold R. Rich
Paul G. Shipley
Frank R. Smith
George B. Wislocki

All correspondence relating to the publication of papers should be addressed to The Editor, Bulletin of the Johns Hopkins Hospital, Baltimore, Md.

Books for review should be sent to The Editor at the above address.

Twenty-five reprints, with covers, of articles will be furnished to contributors free of cost. An order slip for additional reprints, with a table showing cost, is sent with proof.

Correspondence concerning business matters should be sent to The Williams & Wilkins Company, Publishers of Scientific Journals and Books, Mount Royal and Guilford Avenues, Baltimore, Maryland, U. S. A.

This periodical is issued monthly. The current volume is 45. Two volumes a year are issued, each consisting of approximately 400 pages.

Subscription price per volume, postpaid. In the United States and all countries that are members of the Postal Union, $3.00. In countries that are not members of the Postal Union, $3.50. Prices for back volumes and back single numbers on application. Single numbers of the current volume, when available, $.75. Prices are net, postpaid.

New subscriptions are accepted to begin with the current issue, unless the subscriber gives instructions to begin the subscription with some other issue. If the subscriber desires, back issues of the current volume may be obtained when in stock. The publishers do not guarantee to supply back issues, however.

Renewal subscriptions. To avoid a break in your series, subscriptions should be renewed promptly on expiration. Otherwise it may prove impossible for the publishers to furnish the back issues missed, as only sufficient copies are printed of each issue to supply orders in hand.

AGENTS

For Argentina and Uruguay: Beutelspacher y Cia, Sarmiento 815, Buenos Aires.

For Australia: Stirling & Co., 317 Collins St., Melbourne, or G. Jervis Manton, 430 Lit. Collins St., Melbourne (and at Sydney and Brisbane).

For the British Empire, except Australia and Canada: Ballière, Tindall & Cox; 8 Henrietta Street, Covent Garden, W. C. 2, London.

For Canada: Wm. Dawson & Sons, Ltd., 87 Queen Street East, Toronto.

For China: Commercial Press, Ltd., Paoshan Road, Shanghai, China.

For Denmark: H. Hagerup's Boghandel, Gothersgade 30, Kjöbenhavn.

For France: Emil Bougault, 48 Rue des Ecoles, Paris.

For Germany: B. Westermann, Zimmerstrasse 35-41, Berlin N. W., Germany

For Holland: Scheltema & Holkema, Rokin 74–76, Amsterdam.

For Japan and Korea: Maruzen Company, Ltd. (Maruzen-Kabushiki-Kaisha), 6 Nibonbashi Tori-Nichome, Tokyo; Fukuoka, Osaka, Kyoto, and Sendai, Japan.

For Spain: Ruiz Hermanos, Plaza de Santa Ana, 13, Madrid.

THE WILLIAMS & WILKINS COMPANY

Publishers of Scientific Books and Periodicals

BALTIMORE, U. S. A.

Publishers of: *Medicine, Journal of Urology, Bulletin of the Johns Hopkins Hospital, Journal of Pharmacology and Experimental Therapeutics, American Journal of Tropical Medicine, Journal of Immunology. Journal of Industrial Hygiene, Quarterly Review of Biology, Journal of Bacteriology, Annals of the Pickett-Thompson Research Laboratory, Journal of Biological Chemistry, Chemical Reviews, Journal of Dairy Science, Soil Science, Social Forces, Personnel Journal, Journal of Comparative Psychology, Mental Measurement Monographs, Studies in Psychology and Psychiatry, Occupational Therapy and Rehabilitation, American Speech.*

Rapidity of bactericidal action
Absence of stain or odor
Safety—Accidental poisoning impossible

- - - are important features of

HEXYLRESORCINOL SOLUTION S. T. 37

as an antiseptic gargle or spray in the prophylaxis and treatment of infections of the respiratory tract.

As a Gargle or Throat Spray--

May be used full strength or diluted with one to three volumes of water.

As a Nasal Spray—

Dilute with three volumes of warm water.

Supplied in three and twelve ounce bottles.

SHARP & DOHME
BALTIMORE

New York Chicago Kansas City New Orleans San Francisco St. Louis Boston Atlanta Dallas Philadelphia

AT THE MENOPAUSE

The distressing symptoms that so often accompany the climacteric, but more particularly the aggravated symptoms of the artificial menopause, are frequently controlled by the administration of

LUTEIN TABLETS, H. W. & D.
LUTEIN SOLUTION AMPULES, H. W. & D.

The choice of the medication depends, of course, on the judgment of the physician as to whether oral or hypodermatic administration is indicated. Both products represent the

CORPUS LUTEUM OF THE SOW

Lutein Tablets, H. W. & D., are unmodified by treatment with solvents or by exposure to temperatures above animal body heat in the drying process. All separation of extraneous matter is made by mechanical means and all drying is *in vacuo*. The unaltered *corpus luteum* should, therefore, be presented in our products and clinical experience with them should demonstrate their therapeutic activity.

Ovarian dysfunction as evidenced in dysmenorrhea and amenorrhea is also an indication for Lutein medication. Where the diagnosis of such dysfunction was well established, definite therapeutic results have been reported.

WHOLE OVARY TABLETS, H. W. & D.
OVARIAN RESIDUE TABLETS, H. W. & D.

are also offered for those who prefer, for certain indications, the use of the whole gland or of the residue remaining after corpus luteum separation.

Literature furnished on request

H. W. & D.—SPECIFY—H. W. & D.—SPECIFY—H. W. & D.—SPECIFY—H. W. & D.

HYNSON, WESTCOTT & DUNNING : : Baltimore, Md.

Left: Cod with enlarged Liver

Below: Prime Livers constitute 1/7 the weight of the Cod

Food of the Newfoundland Cod makes Vitamin Potency in Cod Liver Oil

THIS is a typical cod, the liver of which is used in the making of Mead's Standardized Cod Liver Oil—plain and flavored. The belly is enlarged with a huge liver—1/7 the weight of the fish. *One seventh the weight of the fish* from which the oil is rendered in the proportions of 3 gallons of oil from 5 gallons of livers, when the fish are in the best physiological condition.

In Newfoundland, Cod Liver Oil production under the Mead Johnson policy is a leading industry. Codfish, dried, are by-products. Quite the reverse from other fisheries. The Newfoundland Cod after a season of gormandizing on caplin, squid, herring and sea plant life or algae, are in excellent condition for oil production.

Food in abundance—as high as 52 caplin have been found in the stomach of a single cod—is converted into a biologically certain, potent, vitamin-containing cod liver oil.

Biological Assay

Biological assay in the laboratories of Mead Johnson and Company tests the potency of each batch of Mead's Cod Liver Oil. Rats are used. After a rickets-producing diet, advanced healing must be shown in 5 days according to the Shipley line test.

MEAD JOHNSON & COMPANY

Evansville, Indiana

Samples and Literature on Request

Oil on way to market

Caplin

A Squid

Entered as second-class matter at the Baltimore, Md., Postoffice. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917. Authorized on July 3, 1918.

Copyright, 1929, by The Williams & Wilkins Company.

JUL 5 1929

BULLETIN

OF THE

JOHNS HOPKINS HOSPITAL

(THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL)

(SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY)

Vol. XLV, No. 1 JULY, 1929

Contents

A Case of Hypophyseal Tumor with Associated Tumor-like Enlargement of the Parathyroids and Islands of Langerhans. PUTNAM C. LLOYD, M.D. 1

John Hunter, His Enemies and His Friends. MANFRED S. GUTTMACHER 15

A Case of Bundle Branch Block Confirmed by Pathological Study. HELEN B. TAUSSIG, M.D. 40

Nervous Control of the Electrical Resistance of the Skin. CURT P. RICHTER 56

PUBLISHED MONTHLY

THE WILLIAMS & WILKINS COMPANY

BALTIMORE, U. S. A.

Made in United States of America